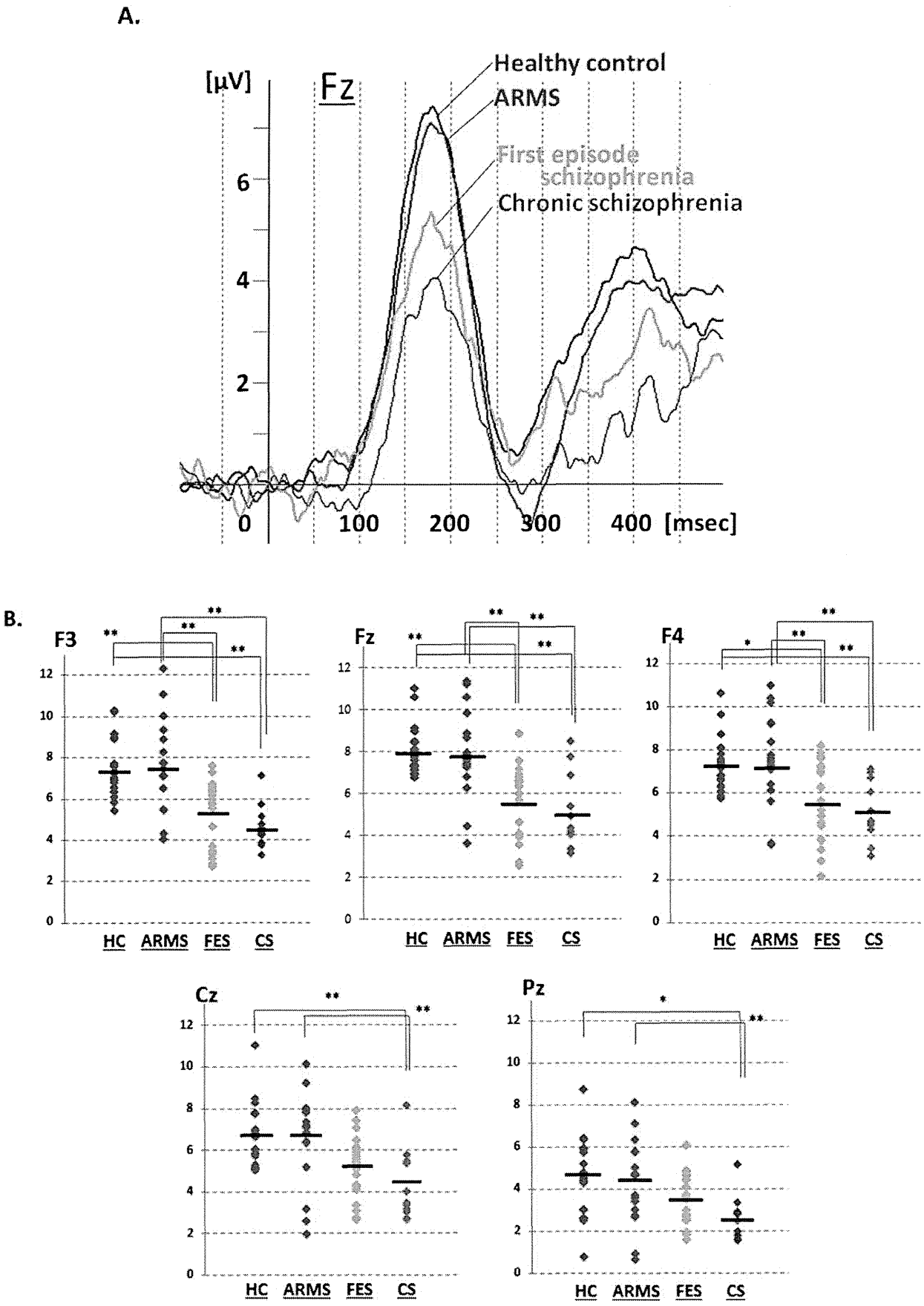

A.
[μV]
Fz
Healthy control
ARMS
First episode schizophrenia
Chronic schizophrenia
6
4
2
0
100
200
300
400 [msec]
B.
F3
Fz
F4
Cz
Pz
HC ARMS FES CS

Figure 1. Duration mismatch negativity (dMMN) waveform at Fz and scatterplots of dMMN amplitudes for all subjects. A. Waveforms are presented for healthy controls (HC, blue line), at-risk mental state (ARMS, red line), first episode schizophrenia (FES, light green line) and chronic schizophrenia (CS, dark green line). B. Distribution of amplitudes are presented for healthy controls (HC, blue dots), ARMS (red dots), first episode schizophrenia (light green dots) and chronic schizophrenia (dark green dots). * $p<0.05$ and ** $p<0.01$, compared to each groups.
doi:10.1371/journal.pone.0054080.g001

records. Subjects with a current history of substance abuse or dependence, seizure or head injury were excluded from the study. Eligible patients had a complete physical examination and standard laboratory testing was normal. Demographic data at baseline evaluation are shown in Table 1.

ARMS subjects were followed-up continuously at the hospital. Four out of the 17 ARMS subjects transitioned to schizophrenia during the observation period. When DSM-IV criteria were met, e.g. auditory hallucinations persisted or any delusion (for example, disturbance of the self) clearly observed, the subject was regarded to have converted to schizophrenia (converters; Conv.). Subjects who did not develop psychosis were defined as non-converters (Non-C.). The average observation period for ARMS subjects was 2.1±1.1 (Non-C.; 1.6±0.8) years.

Clinical Assessment

The Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS) [49] were administered by an experienced psychiatrist. These data are shown in Table 1.

Neuropsychological Assessments

Neuropsychological performance, measured by the Japanese version of the BACS (BACS-J) [8], was evaluated by experienced psychiatrists or psychologists. The BACS-J cognitive battery uses the following assessments in the respective targeted domains: list learning (verbal memory), digit sequencing task (working memory), token motor task (motor function), category fluency and letter fluency (verbal fluency), symbol coding (attention and processing speed), and the Tower of London test (executive function), as shown in Table 1.

Electroencephalogram Recording

Electroencephalograms (EEGs) were recorded based on the previous report of our laboratory [20,30,50,51,52,53]. A 32-channel DC-amplifier (EEG-2100 version 2.22J,Nihon Kohden Corp., Tokyo, Japan), according to the international 10–20 system was used, and recordings were performed using an electro cap (Electrocap Inc., Eaton, OH) in a sound-attenuated room. Data were collected with a sampling rate of 500 Hz. All electrodes were referred to the average amplitude of the ear electrodes (bandwidth = 0.53–120 Hz, 60 Hz notch filter). Electrode impedance was less than 5 kΩ.

Measurements of dMMN were based on our previous report [53]. One thousand auditory stimuli were delivered binaurally through headphones with inter-stimulus intervals 500 msec. Standard/target tones of 50/100 msec duration were randomly presented with the presentation probability of 0.9/0.1. All tones were 60 dB, 1000 Hz and with a rise-fall time of 10 msec. The subjects were requested to watch silent animation movie (Tom and Jerry) and pay attention to the monitor and ignore the tones.

Averaging of ERP waves and related procedures were performed using Vital Tracer and EPLYZER II software (Kissei Comtec, Co. Ltd. Nagano, Japan). Epochs were 600 msec, including a 100-msec pre-stimulus baseline. Eye movement artifacts (blinks and eye movements) were manually rejected. MMN waveforms were obtained by subtract standard waveforms from target ones. ERP component peaks were identified within the 150–250 msec search windows. We selected F3, F4, Fz, Cz and Pz electrodes for analysis, based on our previous report [49].

Statistical Methods

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 19.0 (SPSS Japan Inc., Tokyo, Japan). In order to investigate group differences in MMN, repeated measures analysis of variance (ANOVA) with electrode site as within-subject variable and diagnostic group as between-subject variable was performed. BACS-J domain scores were analyzed with a two-way ANOVA with BACS-J domains as the within factor and group as the between factor. Group×electrode interactions and group×BACS-J domain score interactions were decomposed using one-way ANOVA, with Bonferroni correction. Relationships between MMN amplitudes at the Fz electrode and BACS -J domain scores were analyzed using Spearman rank correlations.

Raters (psychiatrist, psychologist) were not informed of subjects' profiles and diagnosis.

Results

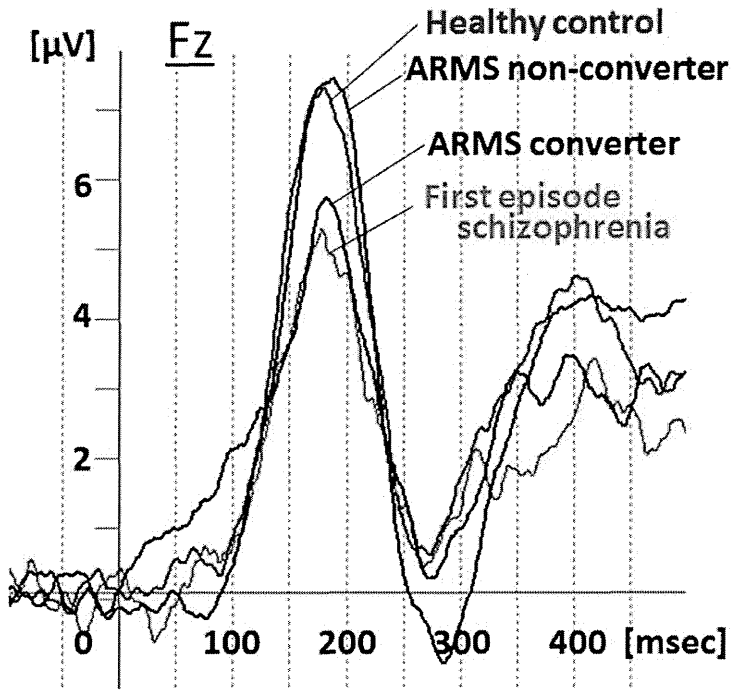
Subjects' Profile

Demographic data of participants are shown in Tables 1 and 2. There was significant group difference in age [$F(3,64) = 5.51$, $p = 0.02$]. The ARMS group was significantly younger than other groups. The female to male ratio in the ARMS group was significantly greater than that in the normal control group [$\chi^2 = 7.94$, $p = 0.004$]. There was no difference between Conv. and Non-C. in age ($p = 0.14$). The male/female ratio of Conv. was greater than Non-C.[$\chi^2 = 4.41$, $p = 0.01$]. Fourteen out of 17 ARMS subjects were not taking any medication, and 3 were prescribed a small dose of risperidone (1.5 mg/day), aripiprazole (6 mg/day), and sulpiride (150 mg/day), respectively, for (or to prevent) acute psychosis episodes (sometimes with strong agitation), based on the criteria of International Early Psychosis Association Writing Group [54]. MMN recordings for these subjects were conducted shortly after medications were started (9, 15 and 27 days). All of the three subjects subsequently developed schizophrenia. Schizophrenia patients were taking the following treatment; FES (no medication 7, risperidone 3, perospirone 3, aripiprazole 2, olanzapine 1, sulpiride 1, blonanserin+quetiapine 1, risperidone+quetiapine 1, risperidone+zotepine 1.), CS (no medication 1, perospirone 3, risperidone 2, olanzapine 2, zotepine 1, perospirone+olanzapine 1, perospirone+aripiprazole 1). There were no differences between ARMS, FES and CS groups in SAPS [$F(2,47) = 0.457$, $p = 0.636$] and SANS [$F(2,47) = 0.118$, $p = 0.889$] scores. Conv. and Non-C. groups did not differ in the SAPS score. However, Conv. group showed a significantly higher score of SANS than Non-C. group (69.0±18.4 vs. 42.9±15.9, $p = 0.02$).

Comparisons of dMMN Amplitudes between Healthy Controls vs. ARMS vs. Schizophrenia

dMMN data are shown in Table 1 and Figure 1. Grand average waveforms in the Fz lead and scatterplots for the electrodes sites are shown in Figure 1A and 1B. ARMS subjects showed dMMN amplitudes similar to those of healthy control subjects. On the

A.


[μV]
Fz
Healthy control
ARMS non-converter
ARMS converter
First episode schizophrenia
6
4
2
0
100
200
300
400
[msec]

B.

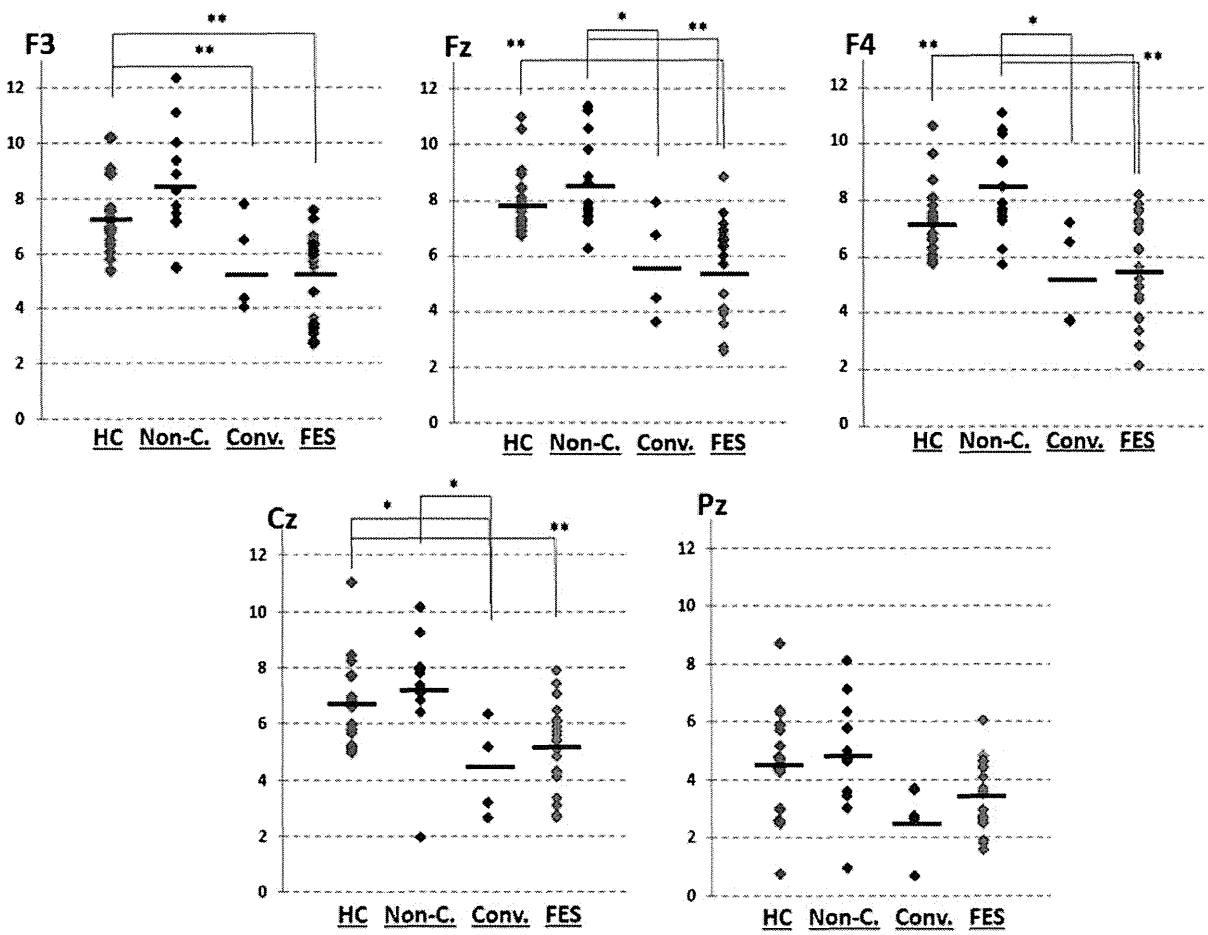

F3
Fz
F4
Cz
Pz
HC
Non-C.
Conv.
FES

Figure 2. dMMN waveform at Fz and scatterplots of dMMN amplitude for at-risk mental state (ARMS,) healthy control (HC) and first episode schizophrenia (FES) subjects. A. Waveforms are presented for healthy controls (blue line), ARMS, converters (Conv.) and non-converter (Non-C.) (black lines), FES (light green line). B. Distribution of amplitudes are presented for healthy controls (blue dots), ARMS, converters (Conv.) and non-converter (Non-C.) (black dots), FES (light green dots). * $p<0.05$ and ** $p<0.01$, compared to each groups.
doi:10.1371/journal.pone.0054080.g002

other hand, FES group showed significantly smaller dMMN amplitudes at frontal electrodes (F3, F4 and Fz). Patients with CS showed greater amplitude reductions at all electrodes compared to healthy controls.

Comparisons of dMMN Amplitudes: Conv. vs. Non-C

Conv. subjects showed significant reduction in dMMN amplitudes at F4, Fz, Cz, and Pz electrode sites compared with Non-C. subjects (Table 2, Figure 2A). Waveforms of Conv. were similar to those of first-episode schizophrenia. By contrast, waveforms of Non-C. resembled to those of healthy controls (Figure 2A). Scatterplots of dMMN amplitudes are shown in Figure 2B. Non-C. subjects elicited larger dMMN amplitudes compared to those of Conv. Amplitudes of Non-C. did not differ from those of healthy controls. On the other hand, Conv. showed significantly smaller dMMN amplitudes at F3 and Cz compared to control subjects. There were no differences in dMMN amplitudes at any electrode between Conv. and FES subjects.

Neuropsychological Measurements: Conv. vs. Non-C

Conv. subjects demonstrated significantly smaller BACS-J scores compared to Non-Conv. subjects for working memory, verbal fluency, and attention (Table 2, Figure 3).

Relationship between Cognitive Performance and dMMN Amplitudes in ARMS subjects

Figure 4 demonstrates correlations between dMMN amplitudes and BACS scores in subjects with ARMS. Significant positive correlations were noted for verbal fluency ($r = 0.546$, $p = 0.02$; Figure 4A), but not other cognitive domains (data not shown). Also, scores of letter fluency task and category fluency task from the BACS-J [55] were significantly correlated with dMMN amplitudes in subjects with ARMS (Figure 4B,C).

Discussion

To our knowledge, this study is the first to report a relationship between dMMN amplitudes and neuropsychological performance in individuals with ARMS. ARMS subjects who later converted to overt schizophrenia elicited reduced dMMN amplitudes at frontal

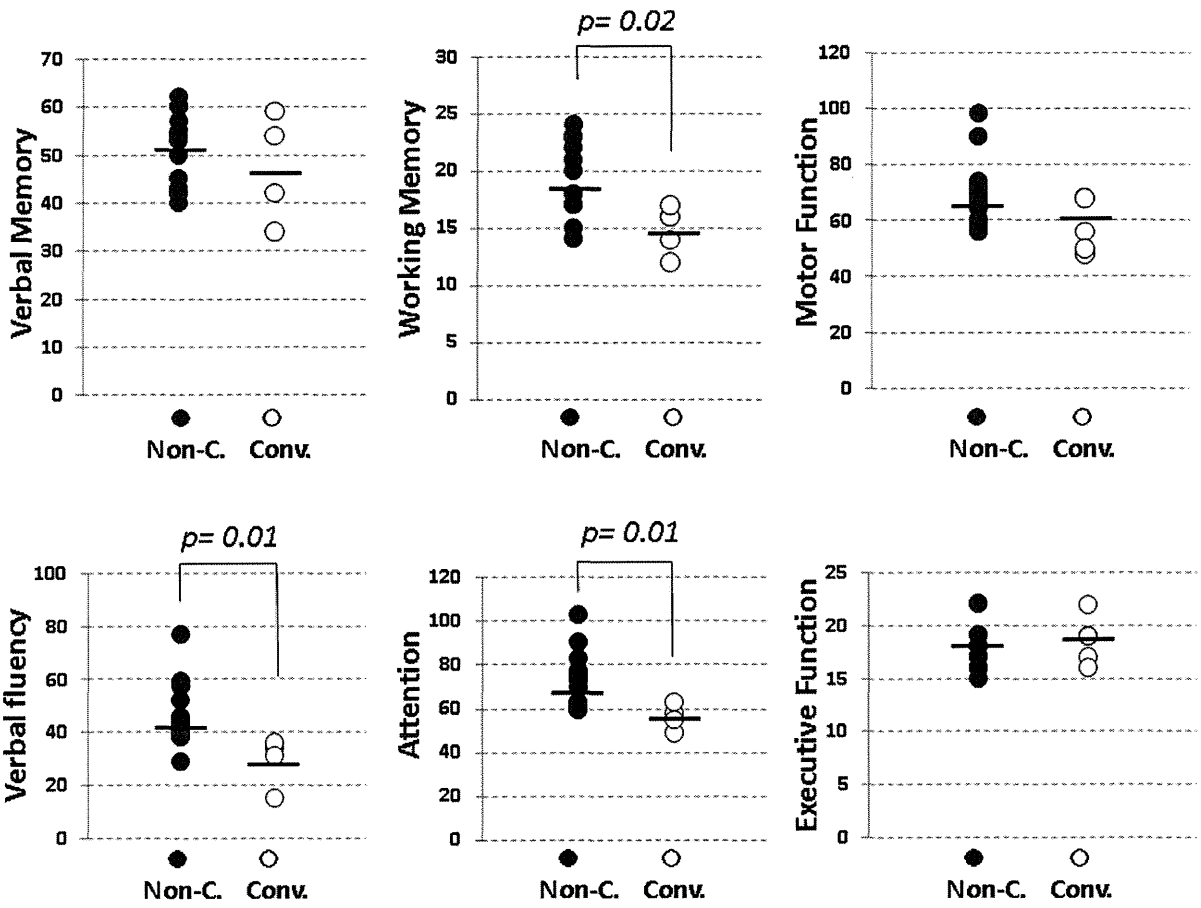


Figure 3. Scatterplot of the score of BACS-J for ARMS subjects. Black symbols(●) and white ones(○) represent scores of non-converters and converters, respectively.
doi:10.1371/journal.pone.0054080.g003

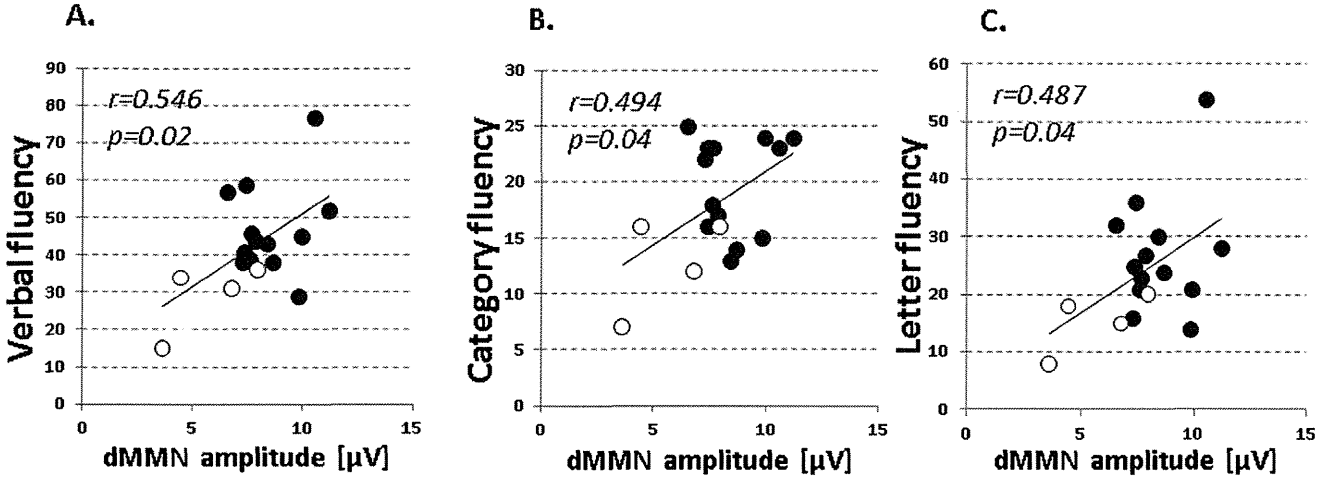


Figure 4. Correlations between dMMN amplitudes at Fz lead and performance on the verbal fluency tasks from the BACS-J in ARMS subjects. Black and white symbols represent scores of non-converters and converters, respectively. Relationships were analyzed using Pearson's product-moment correlation coefficient.
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and central leads compared with non-converters and normal subjects, consistent with previous reports [42,43]. In addition, verbal fluency, working memory and attention/information processing were more greatly impaired in converters compared to non-converters at baseline. Further a significant correlation was noted between performance on verbal fluency tasks and dMMN amplitudes in ARMS subjects. First episode schizophrenia patients showed significantly smaller dMMN amplitudes than ARMS subjects and healthy controls, consistent with previous observations [40,56]. Yung et al. (2003) [57] report that 10–40% of ARMS patients develop schizophrenia, consistent with our observations that 4 out of 17 (23.5%) subjects progressed to overt psychosis. Some previous studies report that ARMS subjects elicit reduced dMMN amplitudes, but with a lesser degree compared to patients with established schizophrenia [40,41,42]. By contrast, dMMN amplitudes of the entire ARMS subjects in the present study were not significantly different from those of healthy controls (Figure 1). One of the reasons for this discrepancy is the difference in age and the percentage of gender, as implicated by some previous studies [32,58,59].

The score of SANS/SAPS of ARMS were similar to schizophrenia (Table 1). We consider it was due, mainly, to the nature of the ARMS subjects studied here. Most of these subjects were referred from PHWCT. The PHWCT, a component of the Consultation and Support Service in Toyama(CAST), includes the Local Support Center for Social Withdrawal Young People that advertises its activity using internet home page and pamphlets. These systems mainly receive consultations from the family members of subjects with social withdrawal and/or disability. This may be why the ARMS subjects studied here elicited relatively severe negative symptoms comparable to those in subjects with overt schizophrenia. With regard to SAPS scores, part of the schizophrenia patients in this study had already been medicated, which may have decreased positive symptoms in these subjects. This may make the SAPS scores for ARMS group and schizophrenia groups look somewhat similar.

Compared to non-converters, dMMN amplitudes in converters were significantly reduced at F4, Fz, Cz and Pz leads (Table 2). This finding suggests dMMN amplitudes may be able to differentiate high-risk individuals who convert to schizophrenia from those who do not. Therefore, these electrophysiological findings are expected to facilitate early intervention of schizophrenia.

MMN is a pre-attentional response to a change of stimuli, and plays a critical role in establishing learning and memory. This electrophysiological event has been suggested to be generated by the glutamate (Glu)/N-methyl-D-aspartate (NMDA) system [60]. This theory is supported by the observation that administration of an NMDA-receptor antagonist (phencyclidine, MK-801 etc.) abolishes MMN in monkeys [61] and rats [62,63]. The pathophysiology of schizophrenia has been shown to be associated with the dysfunction of signal transduction through NMDA receptors [64]. Accordingly, Stone et al. (2009) report that ARMS subjects elicited reduced Glu levels in the thalamus, which was correlated with the gray matter volume of frontal and temporal lobes [65], the brain structures suggested to be involved in MMN generation [66,67]. In fact, the results of the present study (Table 2, Figure 2) indicate the ability of diminished dMMN to predict the development of schizophrenia, as in some previous reports [36–39], suggesting impaired NMDA-mediated transmissions provide an endophenotype for subjects vulnerable to the illness.

Neuropsychological deficits have been shown to exist in the early stage of schizophrenia [46,47]. In this study, neuropsychological performance, as measured by the BACS, differentiated between converters and non-converters in ARMS subjects. Compared with non-converters, scores of working memory, verbal fluency and attention in converters were significantly less for converters (Table 2, Figure 3). These results indicate cognitive abilities, particularly those requiring attention/information processing speed, provides a sensitive marker predicting the development of schizophrenia in vulnerable individuals.

The major finding of the present study was the ability of performance on the verbal fluency tasks to predict dMMN amplitudes in subjects with ARMS (Figure 4). The implications of these observations include the possibility of enhancing accuracy to identify subjects diagnosed with "ultra-high risk" who later develop psychosis. Another advantage is that some neuropsychological tests, which only require a shorter time constraint, could substitute for electrophysiological measurements, e.g. ERPs. In fact, verbal fluency test only requires less than 5 minutes. The easiness of assessment would facilitate the screening for subjects whose psychiatric conditions would not allow them to undergo

ERPs measurement, which generally takes more than 30 minutes. On the other hand, neuropsychological evaluations may sometimes be influenced by motivation of examinees. Therefore, combined administration of neurophysiological and neuropsychological assessments would facilitate screening procedures, depending on the condition of patients. In sum, these efforts are likely to lead to improvement of functional outcome for vulnerable subjects through early intervention by objective probes with greater sensitivity and specificity.

In conclusion, this study confirmed that ARMS subjects who later develop schizophrenia elicit smaller dMMN amplitudes to begin with, compared to non-converters. Notably, we have provided the first evidence for the ability of verbal fluency or attention/information processing to predict dMMN amplitudes in ARMS subjects. These findings are expected to add to the efforts for early diagnosis and intervention of schizophrenia.

Limitations

The main limitations of this study include that ARMS subjects were younger and had a larger female/male ratio compared to other groups. Clearly, further study with a larger number of matched subjects is warranted. Part of ARMS subjects was taking antipsychotic drugs which is another limitation of the study.

The observation periods of Non-C. were relatively short (1.6 ± 0.8 year), compared to similar studies [42,43], which might be another limitation.

Author Contributions

Conceived and designed the experiments: YH T. Sumiyoshi. Performed the experiments: YH T. Seo TM. Analyzed the data: YH YK. Contributed reagents/materials/analysis tools: T. Sumiyoshi MS. Wrote the paper: YH T. Sumiyoshi.

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精神疾患に対する早期介入とその普及啓発に関する研究

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精神疾患に対する早期介入とその普及啓発に関する研究

（H23－精神－一般－009）

At Risk Mental State

ARMS 症例集

At Risk Mental State

Casebook

厚生労働科学研究費補助金

障害者対策総合研究事業（精神障害分野）

精神疾患に対する早期介入とその普及啓発に関する研究

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ARMS 症例集

ARMS 症例集　刊行によせて

本冊子は、厚生労働科学研究費補助金による障害者対策総合研究事業（精神障害分野）「精神疾患に対する早期介入とその普及啓発に関する研究（H23－精神－一般－009)」班において、At Risk Mental State(ARMS)の症例に関する研究のために登録された６１例に関する基本的な症候ならびに背景情報を取りまとめたものです。

ARMS 研究あるいは早期介入の臨床的重要性は、厚生労働省の研究班が組織されることにも象徴されるように、近年広く認識され、世界中でさまざまな研究が進められています。しかしその多くは海外から発信されたもので、受診経路を含めた臨床的背景はわが国の事例とはさまざまに異なります。

統合失調症をはじめとする精神病の前駆状態、あるいはハイリスク状態、発症危険状態などと呼ばれる ARMS の症例を蓄積し、生物科学的な特性の研究を進めるとともに、わが国における臨床家の共通理解を深め、適格な診断とスティグマの低い治療環境の形成、診断・治療ガイドラインの作成、倫理的にも受容可能な臨床サービスのあり方などを考えていくことが求められています。

そのためには専門家が臨床経験を共有し、幅広くディスカッションすることが必要です。

本冊子は、あくまで専門家に研究用資料として活用いただくことを目的としており、各症例の記載に際してはプライバシーに配慮しつつ、連結可能匿名化をしてあります。この点をご了解の上、本冊子をご活用くださいますようお願いいたします。

最後に、日ごろ本研究にご尽力を賜っている分担研究者の諸先生ならびに研究協力者の皆様に心より感謝申し上げます。

平成 25 年 3 月

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Part A
Brief Intermittent Psychotic Syndrome (BIPS)

Part B
Attenuated Positive Symptom Syndrome (APS)

Part A

Brief Intermittent Psychotic Syndrome (BIPS)

【症例番号】NG003
【年齢】15
【性別】男性
【受診日時】X/08/25
【事例化した日時（本人情報）】X/08/20
【事例化した日時（家族情報）】X/08/20
【最初に接触した相談機関】保健所
【その日時】X/08/23

【主訴】ポンポンポンと音がする、ざわざわした人の声がする、何人かで自分のことを噂している
【受診動機】中学時代陸上の選手で、X-1 年の中 3 時の大会の 800m 走でＡ市内 2 位となり、これにより推薦で高校に合格した。成績は中位。小中学では明るい性格であったが、高校に入って、Ｘ年 5 月頃から、だんだん暗くなって、どこかに相談に行きたいと思っていたと母の弁。Ｘ年 8 月 23 日に陸上の練習中に熱中症で倒れ、救急搬送された病院で、頭部ＭＲＩ，血液検査施行されたが異常所見なく、むしろ疎通性の悪さや夜間の異常行動(病室からふらふらと出てくるが、会話が成り立たず、床をみて笑ったりしている、)などがあり、Ｘ年 8 月 25 日に当科外来受診。受診時は小声で、無表情に近い。幻聴、妄想気分、迫害妄想が存在。妄想の影響かすでに陰性症状があるのか、感情表出に乏しく、疎通性不良。精神科入院を勧めたが、母が連れて帰ると強く主張し、リスペリドン（1）1 錠の処方で帰宅する。
【受診経路】救急車⇒救急病院⇒大学病院

【受診に至るまでの相談回数】1 回
【同居者の有無】あり
【保険種別】その他
【母子手帳確認の有無】未確認
【出生時低体重の有無】2200ｇ　保育器に短期間入っていた
【周産期合併症の有無】不明
【運動発達の遅れの有無】なし
【言語発達の遅れの有無】なし
【最終学歴】高校在学中(高校 1 年生)
【学業成績】平均範囲内
【友人の数】平均的
【いじめの有無】一切受けたことがない
【学校内での異常行動の有無】なし
【既往歴】なし
【物質使用歴】なし
【精神疾患家族歴】なし
【現在の GAF】 30
【過去 1 年間における GAF の最高レベル】100

【SOPS による評価】
X年8月20日頃から、外の匂いが気になったり、[ポンポンポンと音が聞こえるようになった]、それで寝付けなくなった。人の声がすることもあり、[ざわざわした人の声がする][何人かで自分のことを噂している]感じがするようになった。何か悪さをされそうな感じもするし、だんだん食欲がなくなった。
P1　不自然な内容の思考=5

質問すると学校でいじめられている感じあるというがはっきりはしない。
P2　猜疑心／被害念慮= 1

はっきりした誇大性は認めない。
P3　誇大性= 0

匂いへの過敏さや聴覚過敏、音へのこだわりあり。
P4　知覚の異常= 5

小声で、弱々しい話し方である。発語せず、うなづくだけの場面も多い。
P5　まとまりのないコミュニケーション= 3
【リスク診断】短期間欠性精神病症状群
【併存診断】器質性精神病疑い（検査上は特定できず）

X+1/12
【移行】なし
【寛解】あり
【処方】なし

【症例番号】　KO002
【年齢】16
【性別】女性
【受診日時】X/10/26
【事例化した日時（本人情報）】X/02
【事例化した日時（家族情報）】X/02
【最初に接触した相談機関】地域総合病院身体科
【その日時】X-1/08
【主訴】人が沢山いると落ち着かない。光がまぶしい。音に敏感。
【受診動機】X 年 1 月末に自宅近くで若い男性からスカートをめくられる事件があり、その後から背後に人がいるのを気持ち悪く感じるようになった。2 月に入ると「人が沢山いると落ち着かない」との訴えが聞かれ始めた。不登校が続き、本人の希望で母親の勤務先である養護学校に転校したが、やはり登校できず、同年代の子供に会うのを嫌い外出もしなくなった為、当院を紹介受診となった。尚、X+1 年 4 月に養護学校高等部に進学するも、「40ｋｇを超えたらデブ」といい、食事量を極端に抑え始め、12 月には 31ｋｇ台まで体重が減少し、入院治療が行われた。
【受診経路】X-1 年の春に中学校 2 年生になってから、「勉強が突然難しくなった」と感じ、10 月頃より週に数日、腹痛などの身体的不定愁訴から学校を休むようになったため、両親の付き添いで 11 月に近医小児科を受診。

【受診に至るまでの相談回数】4 回以上
【同居者の有無】あり
【保険種別】その他不明
【母子手帳確認の有無】未確認
【出生時低体重の有無】なし
【周産期合併症の有無】なし
【運動発達の遅れの有無】なし
【言語発達の遅れの有無】なし
【最終学歴】高校在学中
【学業成績】平均範囲内
【友人の数】少数
【いじめの有無】不明
【学校内での異常行動の有無】不明
【既往歴】なし
【物質使用歴】なし
【精神疾患家族歴】なし

【現在の GAF】 38
【過去 1 年間における GAF の最高レベル】38

【SOPS による評価】
周囲から、なんとなく悪意のある視線を感じるという漠然とした被害関係念慮があった。そのために外出が出来なくなっていた。妄想的確信には至っていなかった。
P1　不自然な内容の思考=5

明らかに猜疑的で警戒しており、面接によって得られる情報はかなり限定されていた。その警戒感により、日常生活においてのセルフケアレベルでの行動も明らかに大きな障害を受けていた。特に男性との関わりを極度に嫌い、根底には妄想的解釈がうかがわれた。
P2　猜疑心／被害念慮= 6

誇大性は認められなかった。
P3　誇大性= 0

「光がまぶしい」と言い、部屋の電気を全て消し、薄暗い中で生活していた。日常生活上の機能低下は明らかで、精神病的であった。また、間歇的な聴覚過敏の訴えも聞かれた。幻聴は認められなかった。
P4　知覚の異常= 6

連合弛緩は認められず、会話の焦点がそれることはなかった。しかし、思考は明らかに鈍かった。返答内容は漠然としたものが多く、目的とする答えを得るためには面接者から直接的な質問が必要であった。
P5　まとまりのないコミュニケーション= 2
【リスク診断】短期間欠性精神病症状群
【併存診断】神経性無食欲症、社交不安障害

X+4/01
【移行】あり　X/12/10
【寛解】なし
【処方】ジプレキサ 10mg