Contribution of the brain-derived neurotrophic factor and neurometabolites to the motor performance

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ABSTRACT

Individual motor performance ability is affected by various factors. Although the key factor has not yet completely been elucidated, the brain-derived neurotrophic factor (BDNF) genotype as well as neurometabolites may become contributing factors depending on the learning stage. We investigated the effects of the Met allele of the BDNF gene and those of the neurometabolites on visuomotor learning. In total, 43 healthy participants performed a visuomotor learning task consisting of 10 blocks using the right index finger (Val66Val, n = 15; Val66Met, n = 15; and Met66Met, n = 13). Glutamate plus glutamine (Glx) concentrations in the primary motor cortex, primary somatosensory cortex (S1), and cerebellum were evaluated using 3-T magnetic resonance spectroscopy in 19 participants who participated in the visuomotor learning task. For the learning stage, the task error (i.e., learning ability) was significantly smaller in the Met66Met group compared with that observed in the remaining groups, irrespective of the learning stage (all p values < 0.003). A significant difference was observed between the Val66Val and Met66Met groups in the learning slope (i.e., learning speed) in the early learning stage (p = 0.048) but not in the late learning stage (all p values > 0.54). Moreover, positive correlations were detected between the learning slope and Glx concentrations in S1 only in the early learning stage (r = 0.579, p = 0.009). The BDNF genotype and Glx concentrations in S1 partially contribute to interindividual variability on learning speed in the early learning stage.

1. Introduction

Fine motor skills/performance is frequently required in our daily lives. Activation of cortical areas such as the primary motor cortex (M1), premotor cortex, supplementary motor cortex, cerebellar cortex, and basal ganglia is particularly important for acquiring motor performance [1]. Among these areas, the neural network mechanisms located on M1 has widely been investigated in humans and animals. For instance, the ability to acquire motor performance has strongly been associated with synaptic plasticity at both excitatory and inhibitory synapses in the M1 [2]. By contrast, it is widely known that a considerable interindividual heterogeneity exists in the capacity of individuals to learn [3,4]. Although motor performance is affected by various factors, these factors have not yet been completely understood.

The brain-derived neurotrophic factor (BDNF) genotype may contribute to the individual variability via synaptic transmission involving glutamate and gamma aminobutyric acid (GABA). BDNF is a member of the neurotrophin family that is expressed throughout the...
central nervous system and plays a vital role in synaptic plasticity [5]. Synaptic plasticity occurs in M1 via glutamatergic and GABAergic synaptic transmissions when we acquire new motor skills [2]. At the molecular level, the BDNF gene contains a functional single-nucleotide polymorphism (rs6265), which results in a valine (Val) to methionine (Met) substitution at codon 66, leading to significantly reduces BDNF frequency of 0%–72% [9]. Taken together, these findings suggest that the BDNF genotype is commonly associated with motor performance through a difference in synaptic transmission. However, controversy remains in this regard because several studies that have explored the effects of the BDNF genotype using various motor tasks have failed to report the same results [10–12].

If motor performance depended on the BDNF genotype, differences in the concentrations of neurotransmitters, such as glutamate and GABA, in the cerebral cortex may finally arise owing to individual variability. Some previous studies have reported the presence of a relationship between the motor performance and GABA concentration, but not glutamate concentration, in the sensorimotor cortex [13, 14] using 3-T magnetic resonance spectroscopy (MRS), which can directly evaluate neurometabolite concentrations. However, it has been stated that glutamatergic transmission including AMPA and NMDA receptors strongly contributes to the process of motor learning through long-term potentiation in M1 [2].

It is still unclear whether BDNF genotype and glutamate concentration in the sensorimotor cortex contribute to the skill acquisition process. Previous studies reported that the Met allele did not change or worsen motor performance compared with that in the case of the Val66Val type [10, 11]. Furthermore, MRS studies revealed that glutamate concentration was not associated with motor performance [13, 14], although long-term potentiation in M1 is believed to be induced by the AMPA and NMDA receptors via glutamate in rats [15]. Considering these controversial findings, it would be difficult to draw a definite conclusion. However, no recent study has considered the effect of the learning stage in both of the abovementioned aspects. The transition from the early learning stage (ELS) to the late learning stage (LLS) is characterized by deceleration of the learning speed [1], and different neural networks are involved in ELS and LLS [16, 17]. For instance, neurotransmitter release or neural plasticity depends on the learning stage [15, 17]. In ELS, GABA release decreases at the inhibitory synapses, whereas that of glutamate increases at the excitatory synapses in LLS. Furthermore, the use-dependent plasticity on M1 occurs in LLS but not in ELS. Considering that neural networks are different between these stages, differential effects on motor performance could be observed between the BDNF genotypes depending on learning stages because Met carriers modulate synaptic transmission [7, 8] and neural plasticity [18, 19]. Considering the BDNF genotype, glutamate concentration might be influenced by learning stages. However, previous studies reported that glutamate is not associated with motor performance without learning stage classification [13, 14]. Perhaps, it would be possible to understand different aspects of motor performance by evaluating the learning stage in comparison with previous studies that have reported about the effect of the BDNF genotype or glutamate concentration on motor performance.

In the present study, we investigated the following two aspects that may determine motor performance ability: 1) the effect of the BDNF genotype on the learning stage and 2) the effect of glutamatergic neurotransmitter on the learning stage using 3-T MRS. We evaluated glutamate concentration in M1, the primary somatosensory cortex (S1), and the cerebellum because multiple cortical areas such as left S1 and right cerebellum are reportedly activated with left M1 by right finger movement [20]. We hypothesized that motor performance varies between the BDNF genotypes at ELS but not at LLS because the difference in the neural transmission efficiency via glutamate and GABA between the BDNF genotypes appeared to particularly affect ELS. ELS-related neural plasticity occurs via neural transmissions [2], whereas LLS-related neural plasticity occurs via synapse formation changes [17]. Therefore, the BDNF genotype-related motor performance changes are likely to occur in the case of ELS only. Furthermore, we hypothesized that the excitatory neurometabolite is one of the factors that determines the individual motor performance ability at ELS. Understanding the neurophysiological processes partially contributing to the factors of individual variability in motor performance may provide novel insights into the promotion of their abilities.

2. Methods

2.1. Participants

In total, 43 healthy participants (28 men and 15 women; age (mean ± SD): 22.0 ± 1.8 years, range: 21–33 years) with no history of neurological or mental disorders were recruited for this study. All of them participated in a visuomotor learning task (VLT) experiment. Of the 43 participants, 19 were also recruited into the MRS experiment (13 men and 6 women; age: 22.6 ± 3.2 years)—these 19 participants were involved in both VLT and MR experiments. This study conformed to the Declaration of Helsinki and was approved by the ethics committee of Niigata University of Health and Welfare. Each participant provided written informed consent before participation. Blood samples were collected from 43 participants before the VLT and MRS experiments; the 2 experiments were performed on separate days.

2.2. Genetic analysis

Blood samples were collected from all participants, and genomic DNA was extracted before the VLT and MRS experiments. The samples were analyzed based on the SNP database (BDNF-rs6265) of the National Center for Biotechnology Information. DNA was extracted from blood samples (200 μL) using NucleoSpin Blood Quickpure kit (Macherey–Nagel GmbH & Co KG, Düren, Germany). High-molecular-weight genomic DNA was isolated using the standard protocol as per the manufacturer’s protocol. The region containing the single nucleotide polymorphism in the BDNF gene was amplified by polymerase chain reaction using CFX connect (Bio-Rad Laboratories, California, USA). Genotype discrimination was automatically performed using Bio-Rad CFX manager 3.1 software. All participants were classified into the Val66Val, Val66Met, and Met66Met BDNF genotype groups.

2.3. Surface electromyography

Electromyography (EMG) was performed using disposable Ag/AgCl electrodes placed over the right first dorsal interosseous muscle in a belly–tendon montage. A ground strap was attached around the right wrist. EMG recordings were sampled at 4000 Hz using an A/D converter (Power Lab 8/30, AD Instruments, Colorado Springs, CO, USA) with 100× amplification (A-DL-720-140, 4 Assist, Tokyo, Japan) and band-pass-filtered between 20 and 1,000 Hz.

2.4. VLT

Participants performed VLT by isometric muscle contraction toward abduction for the right index finger [21, 22] (Fig. 1A). They sat on a chair with a headrest and placed their right upper limbs on a desk. A ring tensiometer (Force link 9311B, Kistler, Winterthur, Switzerland) was tightly fastened on the desk. Participants placed their right index fingers into the ring tensiometer maintaining contact with the distal interphalangeal joint and the ring tensiometer. Data including individual tension were output to a personal computer using the force control software (Niigata Prefecture Industrial Technology Research Institute, Niigata,
Before beginning the task, they were instructed to maintain the maximum muscle contraction of the right index finger toward abduction for 5 s. We defined the mean value calculated from 1 to 4 s as the individual maximum tension. When VLT was initiated, a target marker displayed on the screen moved up and down sequentially (Fig. 1B, C, and D). Participants controlled a control marker according to the abduction force through the ring tensiometer. In the present study, VLT was performed between 0% and 20% force, with the maximum peak of tension set from 10% to 20%. Five movement velocities were set at 5.0, 2.5, 1.66, 1.25, and 1.0 s (Patterns A, B, C, D, and E, respectively), wherein these numbers indicated the time that the target marker moves up and down from the start point to the start point. The sequence-combined movement intensity and movement velocity were sequentially randomized between participants (Fig. 1E). We used the same task sequence (movement intensity × movement velocity) between blocks within participants. Participants were instructed to accurately track the moving target marker using the control marker. This task consisted of 10 blocks (1 block = 35 s; number of movements = 15). A 30-s rest was provided to all participants in each block.

2.5. MR data acquisition

All MR images of each participant were recorded on the same day in the supine position and in the following order: structural magnetic resonance imaging (MRI), functional MRI, and MRS. The magnetic resonance data were acquired using a 3-T Vantage Galan MRI scanner (Canon Medical Systems, Tochigi, Japan) equipped with a 32-channel head SPEEDER coil. Anatomical images were measured using a T1-weighted 3D magnetization-prepared rapid gradient echo sequence with the following parameters: TR = 5.8 ms, TE = 2.7 ms, FA = 9°, TI = 900 ms, slice thickness = 1.2 mm, field of view = 23 × 23 cm², acquisition matrix = 256 × 256 mm², number of slices = 160, and a nonslice gap.

Functional MRI was performed to determine the M1 hand area in the following echo planar imaging sequence: TR = 2000 ms, TE = 25 ms, FA = 85°, slice thickness = 3 mm, field of view = 24 × 24 cm², acquisition matrix = 64 × 64 mm², number of slices = 30, and a nonslice gap.
matrix = 64 × 64 mm², number of slices = 34, and a slice gap = 1 mm. Participants repeatedly tapped their right index finger at a frequency of 1.0 Hz. Maximum activation of the left M1 was determined by analyzing the BOLD signal before MRS recording. The S1 hand area was identified based on the location of the left M1 hand area and the central sulcus. The upper voxel of the right cerebellum was set at the top of the right cerebellum.

MRS data were obtained using a point-resolved spectroscopy sequence (PRESS) suitable for the reliable detection of glutamate plus glutamine (Glx) concentrations with the following parameter settings: TR = 2000 ms, TE = 32 ms, 128 averages for each region, voxels of interest over left M1 and left S1 covering 15 × 15 × 15 mm³, and voxel of interest over the right cerebellum covering 10 × 20 × 20 mm³. Full width at half maximum (FWHM) > 15 Hz for M1 and S1 voxels and 30 Hz for cerebellum voxel were removed from the data.

2.6. Analysis of VLT data

To express the ability of the learning task, we used the task error in each movement velocity condition (5.0, 2.5, 1.66, 1.25, and 1.0 s) at each block (blocks 1–10) [21,22]. The analysis software for VLT displayed the indicated and actual measurement values. The error was calculated using the difference between these values and the absolute value at each timepoint. The sum of the error values measured at each timepoint over the 5% error was calculated and then divided by the maximum individual tension to express the task error. Finally, we used the task error (arbitrary units) to evaluate the motor performance.

The task error at each block was normalized by that at block 1 after calculating of the sum of each block for five sequences. Next piecewise linear regularization analysis was used to estimate the division point between ELS and LLS as described previously [16]. The task errors of ELS and LLS were calculated using the averaged value at each stage. Similar to the task error at each learning stage, the learning slope was estimated at each learning stage by linear fitting [24] to evaluate the speed of the learning process.

2.7. Analysis of MRS data

MRS data were analyzed using the LCModel software (version 6.3-1 M). An LCModel analysis was used to quantify the concentration of neurochemicals within the chemical shift range of 0.2–4.0 ppm. Glx concentrations were automatically calculated for each voxel. Glutamate is referred to as Glx concentration because the spectra overlap and are difficult to reliably distinguish [25]. Glx concentration is expressed as a ratio to total creatine (creatinine plus phosphocreatine, tCr) as the internal reference [14,26]. The exclusion criteria for the data were as follows: Cramer–Rao lower bound (CRLB) value > 10%.

2.8. Statistical analysis

Statistical analysis was performed using the PASW software, version 25 (SPSS, IBM, Armonk, NY, USA). Data normality was evaluated using Kolmogorov–Smirnov tests before the analysis, with log transformation being applied when a violation was identified. For clarity, data are displayed in the nontransformed form [27].

Age was compared among the BDNF genotypes using one-way ANOVA. The task error of all participants without BDNF genotyping were evaluated using a one-factor linear mixed model analysis with repeated measures (LMMRM) with the following configuration: repeated covariance type, AR (1); fixed effect, BLOCK NUMBER (blocks 1–10); random effect, SUBJECT; and method, restricted maximum likelihood. For baseline VLT data among the BDNF genotypes, one-factor LMMRM was performed (fixed effect, BDNF GENOTYPE (Val66Val, Val66Met, and Met66Met)). Moreover, the task error among the BDNF genotype across all blocks was evaluated using two-factor LMMRM (fixed effect, BDNF GENOTYPE, and BLOCK NUMBER). Each model included the data averaged at each movement velocity condition. Two-way ANOVA was computed for the normalized task error or slope of the learning stage [BDNF GENOTYPE and LEARNING STAGE (ELS and LLS)]. When a significant primary effect or interaction was detected, a Bonferroni post-hoc analysis was used to test for significant comparison.

A Spearman’s correlation analysis was used to evaluate relationships between Glx/tCr and the normalized task error or learning slope at each stage for each voxel. Comparison of correlation statistics was performed between both learning stages according to previous studies [14,28]. Significance was determined based on a p value of < 0.05, and all data were represented as mean ± standard error of the mean (SEM).

3. Results

All participants completed the experiments, and none complained of muscle fatigue during VLT. Based on genetic analysis, all participants were classified into the Val66Val, Val66Met, and Met66Met genotypes (Table 1). No differences were observed among the BDNF genotypes for age (F2, 40 = 1.273, p = 0.291, partial η² = 0.060). None of the participants were removed in terms of MRS data based on the exclusion criteria by CRLB and FWHM (Table 2). The representative voxel positions and spectra for the left M1, left S1, and right cerebellum are depicted in Fig. 2.

3.1. Effect of the BDNF genotype on motor performance

For all participants without a BDNF genotype group, the task error was significantly different among BLOCK NUMBER (F(9, 1499.014) = 33.233, p < 0.001). For BLOCK NUMBER, the task error at blocks 2–10 was significantly reduced compared with that at block 1 (all p values < 0.001). The task error among the BDNF genotypes at baseline indicated that the motor performance did not significantly vary among the BDNF genotypes (F2, 39.947) = 0.323, p = 0.726).

The task error among the BDNF genotypes across all blocks is illustrated in Fig. 3. The task error was significantly different between BLOCK NUMBER (F(18, 808.094) = 22.159, p < 0.001) and BDNF GENOTYPE × BLOCK NUMBER (F(18, 808.094) = 1.690, p = 0.036); however, task error of BDNF GENOTYPE (F2, 40.000) = 1.251, p = 0.297) was not significant. The task errors were significantly reduced at blocks 4–10 in the Val66Val group compared with those at block 1 (all p values < 0.025). By contrast, the task errors were significantly reduced at blocks 2–10 in the Val66Met and Met66Met groups compared with those at block 1 (Val66Met, all p values < 0.023; Met66Met, all p values < 0.001). Comparison among BDNF genotype groups indicated no significant differences at each block (all p values > 0.07).

3.2. Effect of the BDNF genotype on the learning stage

The normalized task error and slope data for the learning stage are illustrated in Fig. 4. In the learning stage, the normalized task error was significantly different for the BDNF GENOTYPE (F2, 80 = 8.369, p = 0.001).

| Table 1 | Participant information on the BDNF genotype. |
|---------|-----------------------------------------------|
|         | Val66Val | Val66Met | Met66Met |
| Age     |          |          |          |
| Male    |          |          |          |
| Female  |          |          |          |
| MR (n = 19/43) |          |          |          |
| Participants | 6       | 6        | 7        |
| Age     | 22.7 ± 2.7 | 22.2 ± 2.2 | 23.0 ± 4.0 |
| Male    | 5         | 5        | 3        |
| Female  | 1         | 1        | 4        |

Abbreviation: MR, magnetic resonance.
Table 2

crlb and FWHM values.

|          | m1     | S1     | cerebellum |
|----------|--------|--------|------------|
| Crlb     | 6.00 ± 0.24 | 5.16 ± 0.16 | 6.53 ± 0.25 |
| FWHM     | 10.10 ± 0.25 | 9.40 ± 0.37 | 16.46 ± 0.90 |

Values are expressed as mean ± standard error of the mean. Abbreviations: CRLB, Cramer-Rao values; FWHM, full width at half maximum; M1, primary motor cortex; S1, primary somatosensory cortex.

0.001, partial \( \eta^2 = 0.173 \); however, no significant difference in task error was observed between LEARNING STAGE \((F_1, 80) = 3.884, p = 0.052, \) partial \( \eta^2 = 0.046 \) and interaction \((F_2, 80) = 0.505, p = 0.951, \) partial \( \eta^2 = 0.001 \). The normalized task error in the Met66Met group was significantly smaller than that in the Val66Val and Val66Met groups, irrespective of the learning stage \((all p values < 0.003)\); however, no significant difference was detected between the Val66Val and Val66Met groups \((p = 1.000; \) Fig. 4A). By contrast, the learning slope was not significantly different for the BDNF GENOTYPE \((F_2, 80) = 0.411, p = 0.664, \) partial \( \eta^2 = 0.010 \), but a significant difference was observed between LEARNING STAGE \((F_1, 80) = 38.052, p < 0.001, \) partial \( \eta^2 = 0.322 \) and interaction \((F_2, 80) = 3.352, p = 0.040, \) partial \( \eta^2 = 0.077 \). For ELS, the learning slope in the Met66Met group was significantly steeper than that in the Val66Val group \((p = 0.048)\), but no significant difference was observed between the Val66Met and Val66Val groups \((p = 0.745)\) or the Val66Met and Met66Met groups \((p = 0.548; \) Fig. 4B). For LLS, there was no significant difference among the BDNF genotypes \((all p values > 0.70; \) Fig. 4B).

3.3. Relationship between motor performance and Glx concentrations

Results of the correlation analysis are illustrated in Fig. 5. A positive correlation was observed only between the normalized task error at LLS and Glx/tCR in S1 \((r = 0.533, p = 0.019)\); however, correlations were not observed in the other regions \((all p values > 0.28)\). Moreover, there were no correlations between the normalized task error at ELS and Glx/tCR in any of the regions \((all p values > 0.066)\). By contrast, a positive correlation was observed between the learning slope at ELS and Glx/tCR only in S1 \((r = 0.579, p = 0.009)\) and no correlations were detected between the learning slope at ELS and Glx/tCR in the remaining regions \((all p values > 0.31)\) or between the learning slope at LLS and Glx/tCR in any of the regions \((all p values > 0.095)\). Comparison of correlation analysis for the learning stage demonstrated that there was no significant difference between both learning stages in S1 Glx concentrations for the task error \((Z = 1.454, p = 0.073)\), whereas a significant difference was observed between both learning stages in S1 Glx concentrations for the learning slope \((Z = 2.628, p = 0.004)\).

4. Discussion

The present study explored the effect of the BDNF genotype on motor performance at each learning stage and the relationship between motor performance and the excitatory neurometabolite in the motor performance. Our findings demonstrated that learning slope \((i.e., \) learning speed) differed among the BDNF genotype groups in 10 blocks. Of note, we obtained different effects between the task error and slope for the learning stage. The motor performance was superior in the Met66Met group irrespective of the learning stage. By contrast, the learning slope in the Met66Met group was steeper than that in the Val66Val group at ELS but not at LLS. The correlation analysis revealed high Glx concentrations in S1 that negatively influenced both learning indexes; however, only learning slope correlated with Glx concentrations in S1 at ELS.

4.1. Effect of the BDNF genotype on VLT

The speed of skill acquisition in the Met allele groups was significantly faster than that in the Val66Val group in 10 blocks; however, the motor performance at block 10 did not vary among groups. This result implied that although the BDNF genotype influenced the learning slope \((i.e., \) learning speed), the ultimate ability at the final block remained the same. It is predicted that the BDNF genotype-dependent changes in motor performance are derived from BDNF release in the brain. An animal study demonstrated that BDNF release was reduced in the Met allele type from 18 % to 29 % compared with that in the Val66Val type \([6]\), which resulted in less glutamatergic and GABAergic synaptic transmissions \([7,8]\). Considering that motor learning is a result of long-term potentiation in M1 through glutamatergic and GABAergic transmissions, the difference in learning slope may eventually be caused by neurotransmitter modulation via the decrease in BDNF release. Low Glx concentrations in the Met type may prompt the learning process within a relatively short training period, as observed in our previous study \([29]\). An animal study has demonstrated that first-day training decreased the number of neural spikes on membrane potential and action potential \((i.e., \) M1 excitability was decreased), whereas second-day training increased these indexes \((M1 excitability was increased)\) \([2]\). The researchers suggested that the transient decrease in resting membrane potential prevented increased neural activity in the first-day trained rats to avoid a drastic increase in the excitation–inhibition balance. Therefore, low Glx concentrations in the Met allele type may contribute to the enhancement of the learning speed. As another explanation, the difference in brain development among the BDNF genotypes may influence the learning process. Individuals of the Met allele type exhibited greater cortical thickness in M1 compared with that exhibited by those of the Val homozygote type \([30]\). This finding suggests that the greater M1 volume compensates the impaired neurotransmission, thereby resulting in better learning performance. However, as these possibilities were not investigated in the present study, there exists a need for further research.

Similar results on the BDNF genotype were not obtained in previous studies \((i.e., \) motor performance in the Met allele was not changed or worsened compared with that in the Val66Val type) \([10,11]\). Considerable different methods may have affected the results between those previous studies and our study, such as the motor task and BDNF genotyping. In previous studies, a driving-based learning task \([10]\) and a ballistic learning task \([11]\) were used to evaluate motor performance. The use of different learning tasks exerts a strong influence on the result because different M1 excitability changes were observed between the learning tasks depending on model-free and-based learning \([31]\) or the difficulty level of a learning task \([32]\). In addition, we recruited all BDNF genotypes \((i.e., \) Val66Val, Val66Met, and Met66Met\), whereas previous studies recruited only the Val66Val and Val66Met types \([10,12]\). Although the clear factor remains unknown, motor task and BDNF genotyping could affect the outcome.

4.2. Effect of BDNF genotype on motor performance depending on learning stage

The learning stage was not associated with the motor performance in the BDNF genotype, whereas the learning slope depended on the learning stage. These indexes reflect different aspects of motor performance. The task error expresses motor performance ability, and the learning slope expresses the processing speed of skill acquisition. For the motor performance, only the Met66Met group showed greater values compared with the other groups, irrespective of the learning stage. Although different networks were involved in these stages \([1]\), we observed that the motor performance ability was not differently modulated by the BDNF genotype depending on the learning stage. As previously mentioned, BDNF release was the least in the Met66Met type \([6]\), thereby resulting in the greatest ability in the Met66Met allele type.

The learning slope was steeper in the Met66Met group than in the Val66Val group at ELS; this implies that the processing speed of skill acquisition in the Met66Met group was faster than that in the Val66Val...
group at ELS but not at LLS. Although both phases reflect synaptic plasticity, different plasticity mechanisms are involved in these stages. The ability to acquire new motor skills has been strongly associated with plasticity in functional and structural organization of M1 [14, 33]. At functional level, motor training strengthens the efficiency of neural transmission through NMDA and AMPA receptors or GABA release at ELS [2]. By contrast, at the structural level, synapse formation occurs and the number of synapses is reorganized during the late phase of skill acquisition, except at ELS [17]. Therefore, the difference in the learning speed in the BDNF genotype at ELS may contribute to functional plasticity.

Fig. 2. Overview of the voxel positions and representative spectra. A) left M1, B) left S1, and C) the right cerebellum. Abbreviations: Cho, choline; Glx, glutamate plus glutamine; NAA, N-Acetylaspartate; tCr, creatine plus phosphocreatine.
plasticity by changing the efficacy of existing synapses, rather than structural plasticity through synapse formation.

4.3. Relationship between Glx concentrations in S1 and motor performance depending on the learning stage

Only S1 Glx concentration was associated with learning ability and speed in VLT, but not M1 and cerebellum Glx concentration. Several studies have reported that M1 and cerebellum play an important role in motor performance [16,34–36], whereas the contribution of S1 has received less research attention compared with the role of M1 and cerebellum. However, similar to these regions, S1 strongly contributes to motor performance because S1 excitability changes were observed following motor task [37,38]. Furthermore, removal of S1 in monkeys or sensory deficit in patients with myopathy was found to disrupt proper motor control [39,40]. We used a VLT that required sensory information to control muscle exertion precisely, thereby suggesting that S1 contributes to VLT.

The positive correlation observed between S1 Glx concentration and motor performance implied that excessive Glx concentrations in S1 interrupt motor performance ability and speed. As a potential explanation, the inhibitory activity on S1 may be more important for motor performance than the excitatory activity. S1 gates sensory input from the contralateral side of the body, contributing to filtration of irrelevant signals during a motor behavior [41]. An electroencephalography study demonstrated that sensory gating in S1 as well as intracortical inhibition in S1 were increased during power grip [42]. At behavioral level, the somatosensory temporal discrimination threshold was increased during power grip, and a higher threshold was associated with increased intracortical inhibition in S1 [42], suggesting that the inhibitory processes in S1 increase the discrimination threshold to facilitate better performance during motor behavior. Considering that the inhibitory network filters irrelevant signals via the inhibitory activity, excessive Glx concentrations in S1 may disrupt the inhibitory filtration function.

In the present study, no difference was observed between ELS and LLS in the task error. This result implied that excessive S1 Glx concentrations disrupt individual motor performance ability irrespective of the learning stage. Similar to the BDNF genotype data on motor performance (Fig. 4A), the motor performance ability was not influenced by the learning stage, although different mechanisms are involved in these stages. By contrast, the relationship between learning slope and S1 Glx concentrations depended on the learning stage. As previously mentioned, different aspects are involved between the task error (i.e., motor performance ability) and the learning slope (i.e., learning speed), suggesting that the learning speed shows a higher association with the learning stage and the BDNF genotype or Glx concentrations than with the learning ability. Importantly, the present study findings indicated that S1 Glx concentrations at ELS have higher contribution in determining the learning speed than those at LLS. These findings could provide important information that S1 at ELS contributes to learning speed.

4.4. Limitations

There are two limitations to this study. First, we could not recruit all participants who participated in BDNF genotyping in the MRS experiment. The MRS data were analyzed without the BDNF genotype classification owing to the small sample size (n = 6–7). Therefore, we cannot conclude whether the association between Glx and motor performance varies between the genotype groups. Second, we used Glx as an excitatory neurometabolite index. Glx refers to glutamine and glutamate, meaning that Glx might not directly reflect the excitatory neurometabolite. However, glutamate is referred to as “Glx concentrations” as the spectra overlap and it is difficult to reliably distinguish between glutamate and glutamine [25].

5. Conclusion

The present study investigated whether the BDNF genotype and Glx concentrations partially contributed to the determination of individual motor performance variability, despite motor performance being subject to various factors. Our results indicated that the learning speed was faster in the Met66Met group than in the Val66Val group at ELS but not at LLS. Moreover, positive correlations were detected between Glx concentrations and the learning indexes only in S1, indicating that high Glx concentrations in S1 contribute to low motor performance ability and learning speed. By contrast, the learning speed was associated only with ELS but not LLS. Overall, the learning speed may be more sensitive to the BDNF genotype and Glx concentrations than to learning ability. This study provides important neurophysiological information that could help in characterizing variability in the prompt motor performance process.
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Data accessibility statement

Data in this study will be made available upon request from the corresponding author.

Author contributions

H.O. and R.S. conceived the study and designed the experiments. R.S. and H.W. collected VLT data, and K.O., N.S., N.K., H.W., and H.O. collected MR data. R.S. and S.M. performed data interpretation. R.S. and H.O. performed statistical analysis. N.O. and S.M. analyzed BDNF samples. R.S. and H.O. wrote the manuscript. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors report no declarations of interest.

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Fig. 5. Correlations between the motor performance or learning speed at each learning stage and Glx concentrations in S1. Abbreviations: ELS, early learning stage; Glx, glutamate pulse glutamine; LLS, late learning stage; S1, primary somatosensory cortex; tCr, creatine plus phosphocreatine.
