RESEARCH ARTICLE

# BDNF Val66Met polymorphism is associated with altered activity-dependent modulation of short-interval intracortical inhibition in bilateral M1

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## Abstract

The BDNF Val66Met polymorphism is associated with impaired short-term plasticity in the motor cortex, short-term motor learning, and intermanual transfer of a procedural motor skill. Here, we investigated the impact of the Val66Met polymorphism on the modulation of cortical excitability and interhemispheric inhibition through sensorimotor practice of simple dynamic skills with the right and left first dorsal interosseous (FDI) muscles. To that end, we compared motor evoked potentials (MEP) amplitudes and short-interval intracortical inhibition (SICI) in the bilateral representations of the FDI muscle in the primary motor cortex (M1), and interhemispheric inhibition (IHI) from the left to right M1, before and after right and left FDI muscle training in an alternated sequence. Val66Met participants did not differ from their Val66Val counterparts on motor performance at baseline and following motor training, or on measures of MEP amplitude and IHI. However, while the Val66Val group displayed significant SICI reduction in the bilateral M1 in response to motor training, SICI remained unchanged in the Val66Met group. Further, Val66Val group's SICI decrease in the left M1, which was also observed following unimanual training with the right hand in the Control Right group, was correlated with motor improvement with the left hand. The potential interaction between left and right M1 activity during bimanual training and the implications of altered activity-dependent cortical excitability on short-term motor learning in Val66Met carriers are discussed.

## Introduction

Brain-derived neurotrophic factor (BDNF) is abundant throughout the brain [1, 2]. BDNF is largely synthesized through the activation of glutamatergic neurons and modulates pre- and post-synaptic plasticity by regulating glutamatergic excitatory and gamma-Aminobutyric acid (GABA) inhibitory transmission [1–9]. Thus, it is perhaps not surprising that BDNF is involved in long-term potentiation (LTP) and depression (LTD) [6, 8, 10–16], two mechanisms of cortical plasticity that are associated with learning in the primary cortex (M1) [17–

20]. While the most frequent variant of the BDNF gene is Val66Val, recent studies have shown that a single nucleotide polymorphism of the BDNF gene at codon 66 (Val66Met), found in approximately one third of the American population [21], relates to reduced BDNF activity-dependent expression, altered glutamatergic and GABA-ergic synaptic transmission, and altered white matter integrity in the corpus callosum [22–25]. Incidentally, Val66Met carriers exhibit impaired M1 cortical excitability, short-term motor learning, retention and intermanual transfer of a motor skill [26–29].

Transcranial magnetic stimulation (TMS), a non-invasive brain stimulation technique, is widely used to assess activity-dependent changes in intracortical and corticospinal excitability that occur through motor practice [30–35]. Motor Evoked Potentials (MEP) reflect the global changes in cortical excitability via the direct and indirect stimulation of corticospinal fibers as well as spinal cells [20, 36–38]. In addition, GABA-mediated intracortical inhibition mechanisms can be assessed with paired pulse stimulation techniques using short latency and subthreshold pre-conditioning in M1, in a process known as short-interval intracortical inhibition (SICI) [32, 39–43]. Both processes are particularly relevant to manual motor learning and transfer as studies have repeatedly shown, although not systematically [44], increases in MEP amplitudes and decreases in SICI in the M1 contralateral to the trained hand following motor practice, and reduced SICI in the transfer hemisphere [39, 45–47]. Unilateral hand movements with the dominant or the non-dominant hand may also activate bilateral M1 and alter cortical excitability (MEP; SICI) in the homotopic muscle representations in the ipsilateral M1, more so when the non-dominant hand is activated [48–56]. These observations highlight the interhemispheric interactions that occur during motor practice, where the hemisphere contralateral to the trained hand inhibits superfluous activity originating from the opposite hemisphere in a process known as interhemispheric inhibition (IHI) [52, 57–61]. Recent studies have suggested IHI involvement in the intermanual transfer of procedural and sensorimotor learning [45, 47, 62]. Despite advancements on the possible influence of the Val66Met polymorphism on M1 corticospinal excitability, motor learning and intermanual transfer of procedural motor skills, it remains unclear whether the Val66Met polymorphism interferes with activity-dependent modulation of neurophysiological mechanisms that underlie their expression, namely SICI and IHI.

The first objective of the present study was to assess motor learning of low-force sensorimotor skills with the right hand, and their intermanual transfer from the right hand to the left hand, in Val66Val and Val66Met participants. Rapid Tapping (RT), Precision Grip Strength (PGS), and Grooved Pegboard (GPB) tasks were used, as intermanual transfer of these motor skills has been shown in separate experiments [63–67], and since differences in corticospinal excitability in the contralateral M1 has been evidenced between both groups following motor training on similar tasks [26, 28]. Given the absence of reported differences in motor learning on tasks involving sensorimotor adaptations between Val66Val and Val66Met individuals [26–28], it was hypothesized that motor learning with the right, dominant hand would not differ between groups. However, in light of recent data showing reduced intermanual transfer of a procedural motor skill after a single session of motor training in individuals with the Val66-Met genotype [29], it was hypothesized that participants with the Val66Met polymorphism would show impaired intermanual transfer of sensorimotor skills from the right, dominant to the left, non-dominant hand.

The second objective of the present study was to compare neurophysiological mechanisms that underlie motor learning and the intermanual transfer of sensorimotor skills, namely corticospinal excitability and SICI in bilateral M1, and IHI from the left to right M1. It was hypothesized that participants with the Val66Met polymorphism would display reduced modulation of MEP and SICI in the bilateral M1, and IHI from the left to right M1, compared to Val66Val participants.

## Materials and methods

### Participants

**Experiment 1.** Fifty-six right-handed participants aged 18 to 35 years old were recruited for genotyping. Out of the fifty-six participants, thirteen presented the Val66Met polymorphism, three males and ten females. The three males and seven randomly selected females were assigned to the Val66Met group (21.90±2.28 years, 7 women). Participants in the Val66-Val group were matched on gender to control for known interactions between the Val66Met polymorphism and gender on motor control [68]. Thus, three males and seven females were randomly selected and assigned to the Val66Val group (21.90±1.79 years, 7 women). In addition, ten right-handed participants were separately recruited and assigned to the Control-Left group (CL; 23.10±3.75 years, 7 women). The CL group was used to isolate the behavioral effects of motor practice with the left hand to determine the presence of intermanual transfer in the experimental groups who performed the motor tasks with both hands in an alternated sequence.

**Experiment 2 (control).** Ten right-handed participants were recruited in a separate experiment and assigned to the Control-Right group (CR; 24.60±3.77 years, 7 women). This control experiment served two functions: *i)* show that the tasks used in Experiment 1 and executed with the right hand elicited motor learning; and *ii*) show that the tasks used in Experiment 1 and executed with the right hand induced modulation of MEP amplitudes and SICI in the left M1, and IHI from the left to right M1, in the expected directions.

All participants declared being healthy and reported no history of psychiatric or neurological condition, and none presented with contraindications to the safe use of TMS [69]. They provided their written informed consent to undergo experimental procedures approved by the Comité d'Éthique de la Recherche des Sciences de la Santé (CÉRSS) and compliant with the 1964 Declaration of Helsinki.

### Genotyping

The BDNF genotyping method was identical to the procedure described in Morin-Moncet et al. (2014). Briefly, DNA was extracted from the saliva with Oragene OG-250s kits (DNA Genotek, Ottawa, ON, Canada). PCR following an established pyrosequencing protocol [70] was performed to determine the profiling of the BDNF rs6265 (Val66Met) polymorphism.

### Behavioral tasks

Participants were seated comfortably in an upright position facing a computer screen at approximately three feet with the elbows flexed at a 90˚ angle and the wrists resting on a table. The subjects were instructed to perform a series of three motor tasks in a fixed order: RT, PGS, and GPB (see Fig 1). Motor performance with the left hand was measured in two conditions, L1 and L2. L1 was used as a pre-training, baseline measurement of motor performance. L2 served as a measurement of performance following right hand training (R1, R2). L1 and L2 were identical and consisted of three blocks of the RT and the PGS tasks, lasting 30 seconds each, followed by 90 seconds of continuous GPB, for a total of approximately 5 minutes per condition.

Motor training with the right hand comprised two identical conditions, R1 and R2, to assess motor learning. Both conditions consisted of ten blocks of the RT and PGS tasks, followed by five minutes of continuous GPB, for a combined R1 and R2 time of 30 minutes. For the three tasks, a green and red circle appeared in the middle of a computer screen, accompanied by a sound signal, to indicate the Go and Stop signals, respectively. The signal presentation and the
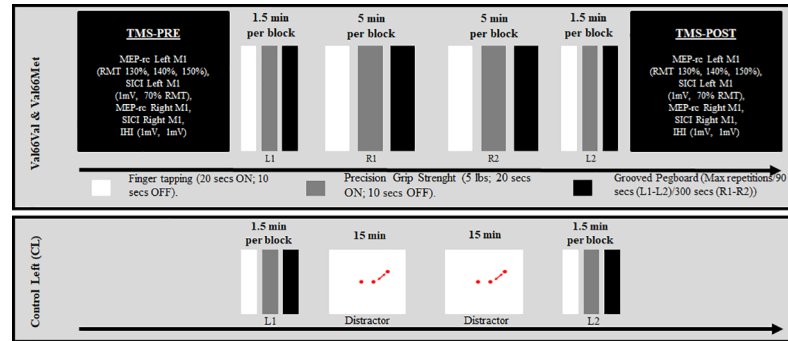
**Fig 1. Experiment 1.** The experimental design used in Experiment 1 is displayed for the Val66Val, the Val66Met, and the Control-Left (CL) groups.

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duration of the blocks were monitored by Presentation software (Neurobehavioral Systems ®, California, USA).

To control for the learning effects resulting from practice with the left hand during L1 and L2, the CL group performed the L1 and the L2 conditions only, separated by a 30-minute period during which participants performed a computerized distractor task. In Experiment 2, the CR group executed R1 and R2 blocks with 5 minutes of the computerized distractor task before and after right-hand training (see Fig 2). The distractor task was run with Psyscope X software running on a 17-inch I-Mac computer (Apple, Cupertino, USA). It was designed to ensure sustained focus and limited motor activity. The task consisted in the presentation of two red dots symmetrically located across the center of the screen. The left dot was static while the right dot moved in a semi-circular, counter-clockwise 90˚ rotation, and back to its original position, at a frequency of 0.5 hertz. Participants were asked to silently count the number of rotations, which varied between 25 and 35 in each block.

Rapid Tapping (RT). Participants were instructed to alternate key presses of the 1 (index finger) and 3 (middle finger) keys on a numeric keypad as fast as possible. Reaction times, representing delays in milliseconds between alternated key presses with the index and the middle finger, were recorded using Presentation software (Neurobehavioral Systems ®, California, USA) and stored off-line for analysis. A single block was defined as 20 seconds of finger tapping followed by 10 seconds of rest for a total of 30 seconds. Reaction times were averaged for the total number of blocks for each condition (L1, R1, R2, L2).

Precision Grip Strength (PGS). Participants were instructed to apply and maintain, as precisely as possible, a pressure of 5lbs using their index and middle finger on a pinch gauge dynamometer (JTech Commander ®, Utah, United States). A single block consisted of 20 seconds of pinch pressure followed by 10 seconds of rest, for a total of 30 seconds. The precision score was computed as the average of the absolute difference between the pressure score and the
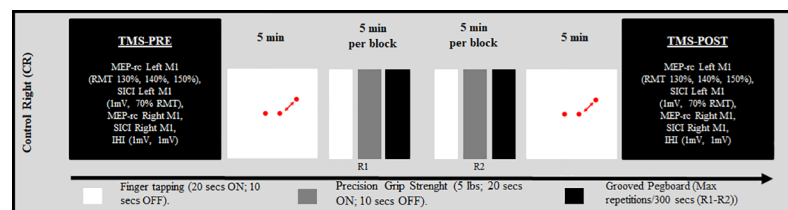


**Fig 2. Experiment 2.** The experimental design used in experiment 2 is displayed for the Control-Right (CR) group.

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target score (5lbs) at each second (1 Hertz) for the total number of blocks on each condition (L1, R1, R2, L2).

Grooved Pegboard (GPB). Two original Grooved Pegboard Tests (Lafayette Instruments ®, Indiana, USA) were used for this task. Participants were instructed to fill up the rows from left to right and top to bottom, one peg at a time, as fast as possible, using their index finger and thumb. They were instructed to ignore dropped pegs and to proceed with the second GPB upon completion of the first. A block consisted of 90 seconds of continuous execution in the L1 and L2 conditions, and in five minutes of continuous execution on the R1 and R2 conditions. A dexterity score was computed as the average time in seconds taken to complete each row, per condition (L1, R1, R2, L2).

## Transcranial magnetic stimulation

TMS pulses were delivered using two 8-cm figure-of-eight coil connected to a Magstim BiStim (Magstim company, Whitland, Wales, UK). The stimulation coils were held posterolaterally at a 45˚ angle from the midline and applied flat on the scalp. For the MEP recruitment curves (MEP-rc) and SICI, a brainsight neuronavigating system (Rogue Research, Montréal, Canada) was used to ensure stable positioning of the coil throughout the experiment. For IHI, the optimal stimulation site of the left FDI muscle over the right M1 was marked on the participants' scalp. MEPs were recorded using bipolar surface electrodes positioned over the left and right FDI muscles, and the ground electrode positioned on the right inner forearm. The electromyographic signal was amplified using a Powerlab 4 / 30 system (ADInstruments, Colorado Springs, USA; gain factor: 1000), filtered with a band-pass 20–1000 Hz, and digitized at a sampling rate of 4 kHz. MEPs were recorded using Scope v4.0 software (ADInstruments, Colorado Springs, USA) and stored offline for analysis. The optimal stimulation site for the bilateral first dorsal interosseous (FDI) muscle representation in M1 was defined as the area on the scalp eliciting MEPs of maximal amplitude in the left and right FDI muscles. Complete relaxation of the FDI muscle was controlled by monitoring the absence of EMG signal up to 100 ms before the TMS pulse. The number of MEPs excluded was marginal (i.e. less than 1%). TMS pulses were delivered with 6–7 seconds inter-stimulus intervals to avoid anticipation. Resting motor threshold (RMT) was determined prior to both TMS sessions, before (session 1: Pre) and after (session 2: post) motor training. RMT was defined as the minimum intensity level of TMS required to elicit MEPs of 50 μV in at least 5 trials out of 10 [71]. Further, the TMS intensity required to elicit MEP amplitudes of ≈ 1 mV on average for ten stimulations at rest was determined before the SICI measurements in the left and right M1. MEP-rc and SICI were measured in sequence, pre- and post- motor training beginning with the left M1. IHI from the left to right M1 was measured last, Pre- and Post- motor practice (see Fig 1).

MEP-rc. Corticospinal excitability was measured first, pre- and immediately post- motor training. The MEP-rc consisted of ten TMS pulses delivered at 130, 140, and 150 percent of the participants' RMT in a semi-randomized order, with an interstimulus interval of 6–7 seconds, for a total of 30 MEPs. These intensities were selected based on previous work on intermanual transfer of motor skill showing significant increases in MEP amplitudes at these intensity levels compared to intensities ≤ 120% RMT [45, 47]. Peak-to-Peak MEP amplitudes were measured and averaged for each intensity level, pre- and post- motor training.

SICI and IHI. For SICI, paired pulse stimulation was delivered with a conditioning stimulus (CS) intensity of 70% of RMT and a test stimulus (TS) intensity at the level required to elicit MEP amplitudes of ≈ 1 mV at rest, with a 3-millisecond interstimulus interval (ISI). While intracortical facilitatory circuits may interfere with SICI at ISIs greater than 2 milliseconds [72], this ISI was selected in accordance with previous experiments [41, 45, 73] to differentiate

between the two phases of inhibition observed at ISIs of 1 millisecond and 2.5 milliseconds, with the latter ISI likely reflecting intracortical GABA-ergic circuitry [32, 74, 75]. IHI from the left to right M1 was assessed with paired CS and TS stimulus intensities set at the level required to elicit MEPs of $\approx$ 1 mV at rest, over the left and right M1, with an ISI of 10 milliseconds. Ten TS were delivered first, followed by ten CS-TS paired-pulse stimulations. Peak-to-peak MEP amplitudes were averaged separately for the ten TS MEPs and the ten conditioned MEPs. SICI and IHI were defined as the percentage of the averaged conditioned MEP amplitudes relative to the averaged TS MEP amplitudes (i.e. $M_{\text{conditioned MEP}} / M_{\text{TS MEP}}$ x100), pre- and post-motor training.

## Data analysis

**Experiment 1.** Motor learning with the right hand in the Val66Val and the Val66Met groups was assessed with three mixed ANOVAs, one for each task (RT; PGS; GPB), with *condition* (R1; R2) as the within-subjects factor and *group* (Val66Val; Val66Met) as the between-subjects factor.

The presence of intermanual transfer from the right dominant hand to the left non-dominant hand was individually measured for each of the three tasks (RT; PGS; GPB) by comparing the performance in L1 and L2 between the Val66Val, Val66Met, and the CL groups. To that end, three mixed ANOVAs were computed, with *condition* (L1; L2) as the within-subjects factor and *group* (Val66Val; Val66Met; CL) as the between-subjects factor.

RMT and 1 mV stimulus intensities, expressed as a percentage of the device's maximal stimulation output, were compared pre- and post- motor practice using two mixed ANOVAs with *hemisphere* (Left M1; Right M1) and *time* (Pre; Post) as the within-subjects factors and *group* (Val66Val; Val66Met) as the between-subjects factor.

MEP-rc was compared pre- and post- motor training between the Val66Val and the Val66Met using mixed ANOVAs with *hemisphere* (Left M1; Right M1), *time* (Pre; Post), and *intensity* (MEP-rc 130; MEP-rc 140; MEP-rc 150) as the within-subjects factors and *group* (Val66Val; Val66Met) as the between-subjects factor. A mixed ANOVA was used to compare SICI with *hemisphere* (Left M1; Right M1) and *time* (Pre; Post) as the within-subjects factors and *group* (Val66Val; Val66Met) as the between-subjects factor. IHI from the left to right M1 was assessed between the Val66Val and Val66Met participants before and after motor practice using a mixed ANOVA with *time* (Pre; Post) as the within-subjects factor and *group* (Val66Val; Val66Met) as the between-subjects factor. In addition, a mixed ANOVA with *hemisphere* (Left M1; Right M1) and *time* (Pre; Post) as within-subjects factors and *group* (Val66Val; Val66Met) as between-subjects factor was computed to compare test MEP amplitudes in SICI. A similar procedure was applied for IHI from the left to right M1, without the *hemisphere* factor.

Normality of the standardized residuals distributions of the TMS and behavioral variables used to compare Val66Val and Val66Met participants was assessed with Kolmogorov-Smirnov and Shapiro-Wilks tests. Non-normal variables were transformed with log10 computations and were reanalyzed with the same procedure as described above.

Finally, intraclass correlation coefficients (ICC) were measured for TMS variables (e.g. RMT: MEP-rc; SICI; IHI) in Val66Val and Val66Met groups separately to insure both samples representativeness based on intersession reliability scores in other experiments [76–80]. Intersession ICCs were obtained with a two-way mixed-effects model. ICCs were interpreted as follows: Excellent: ICC > 0.75; Good: $0.75 \geq$ ICC $\geq 0.59$; Fair: $0.58 \geq$ ICC $\geq 40$; Poor: ICC > 40 [76, 81].

**Experiment 2.** The presence of motor learning in the CR group was assessed by comparing performance on the RT, PGS, and GPB tasks on R1 and R2 conditions with separate

paired-samples t-tests. RMT and 1 mV stimulus intensities were compared, before and after motor training in the left and right M1, with a mixed ANOVA with *hemisphere* (Left M1; Right M1) and *time* (Pre; Post) as the within-subjects factors. MEP-rc and SICI were compared Pre- and Post- motor training using a mixed ANOVA with *hemisphere* (Left M1; Right M1), *time* (Pre; Post), and *intensity* (MEP-rc 130; MEP-rc 140; MEP-rc 150) as the within-subjects factors for the MEP-rc, and *hemisphere* (Left M1; Right M1) and *time* (Pre; Post) for SICI. IHI from the left to right M1 was compared before and after practice with a paired-samples t-test. Test MEP amplitudes were compared for SICI using a mixed ANOVA with *hemisphere* (Left M1; Right M1) and *time* (Pre; Post) as within-subjects factors, and with a paired-samples T-test for IHI. Post-hoc analyses were conducted, as necessary, using contrasts with Bonferroni correction on the repeated measures models and with Tukey HSD for between-subjects comparisons. Bilateral Spearman correlations between measures of neurophysiological activity and motor performance were performed as necessary. $\alpha = 0.05$.

## Results

### Experiment 1

**Behavioral.** Learning with the right hand (see Fig 3A, 3B and 3C). Mixed ANOVAs revealed a significant effect of *condition* on the RT ($F_{(1, 18)} = 10.244$; $p = 0.005$) and GPB tasks ($F_{(1, 18)} = 32.767$; $p < 0.001$), with no significant effects of *group* ($F_{RT (1,9)} = 0.282$; $p = 0.602$; $F_{GPB (1, 9)} = 0.598$; $p = 0.45$) or *condition* x *group* interaction ($F_{RT (1,9)} = 1.654$; $p = 0.215$; $F_{GPB (1, 9)} = 1.629$; $p = 0.219$). For the PGS task, the effects of *condition* ($F_{(1, 18)} = 0.448$; $p = 0.512$), *group* ($F_{(1, 18)} = 0.11$; $p = 0.744$), and the *condition* x *group* interaction ($F_{(1, 18)} = 0.567$; $p = 0.461$) were not significant.

Transfer to left hand (see Fig 3D, 3E, and 3F). For the left-hand conditions, a participant in the Val66Met group was excluded from RT measurements due to technical difficulties during data acquisition. As a result, for the RT task, the CL, Val66Val and the Val66Met groups comprised 10, 10, and 9 participants, respectively. For the RT task, a mixed ANOVA revealed a significant effect of *condition* ($F_{(1, 26)} = 7.212$; $p = 0.012$) with no *group* ($F_{(2, 26)} = 1.237$; $p = 0.307$), or *condition* x *group* interaction ($F_{(2, 26)} = 2.499$; $p = 0.102$) effects. For the GPB task,
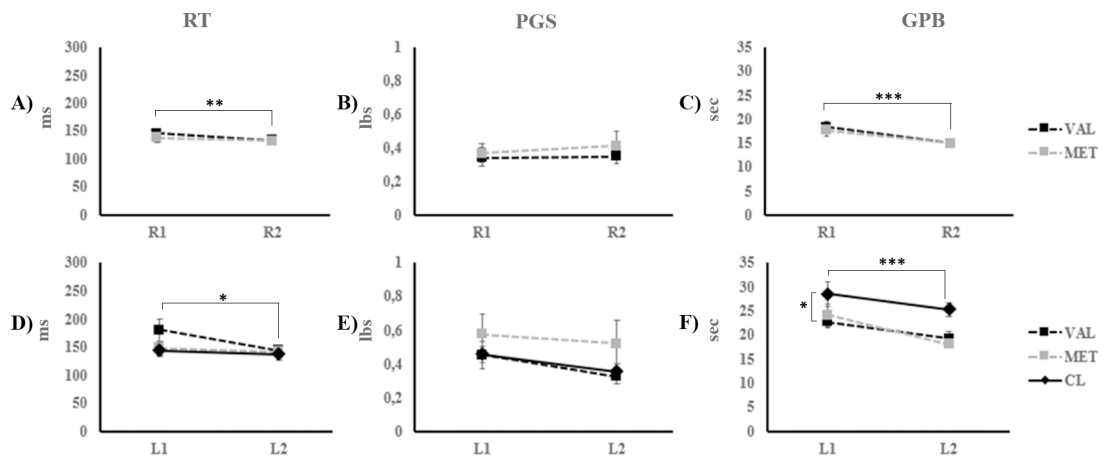


**Fig 3. Motor performances on the rapid tapping (RT), pinch grip strength (PGS), and the grooved pegboard (GPB).** The mean scores on the RT, the PGS, and the GPB are presented for the Val66Val and the Val66Met participants in Experiment 1 on the R1 and R2 conditions with the right hand (A, B, and C, respectively), and the L1 and L2 conditions with the left hand (D, E, and F, respectively). The error bars represent standard errors of the mean. Full lines used for comparisons represent main effects. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

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there was a significant effect of *condition* (F = 16.082; p < 0.001) and *group* (F = 4.399; p = 0.022) while the *condition* x *group* interaction was not significant ($F_{(2, 27)}$ = 0.71; p = 0.499). Post-hoc comparisons revealed slower responses in CL participants compared to Val66Met participants (p = 0.031), with no other difference between groups (all p > 0.05). For the PGS task, the effects of *condition* ($F_{(1, 27)}$ = 3.516; p = 0.072), *group* ($F_{(2, 27)}$ = 1.15; p = 0.332), and the *condition* x *group* interaction ($F_{(2, 27)}$ = 0.219; p = 0.805) were not significant.

In sum, all three groups exhibited improved performance with the left hand on L2 compared to L1 on the RT and the GPB tasks. Moreover, improvements on L2 in the Val66Val and Val66Met groups did not differ from that of the CL group, suggesting an absence of significant skill transfer from the right to the left hand.

**TMS.** RMT and 1 mV intensity. A mixed ANOVA was used to compare RMT intensities before and after motor practice between the Val66Val and Val66Met and revealed a significant effect of *hemisphere* ($F_{(1, 18)}$ = 5.934; p = 0.025), while the effects of *time* ($F_{(1, 18)}$ = 0.488; p = 0.494) and *group* ($F_{(1, 18)}$ = 0.018; p = 0.895) were not significant. Stimulus intensities used to elicit MEPs at the RMT did not differ before and after motor practice, without distinction between genetic groups, and were generally lower in the left M1 compared to the right M1. For 1mV, stimulus intensities did not differ before and after motor practice ($F_{(1, 18)}$ = 2.592; p = 0.125), between the left and right M1 ($F_{(1, 18)}$ = 2.029; p = 0.171), or between groups ($F_{(1, 18)}$ = 0.031; p = 0.862). None of the interactions for the RMT and 1mV measurements were significant ($0.04 \leq F \leq 1.893$; $0.186 \leq p \leq 0.844$).

MEP-rc (see Fig 4A). A mixed ANOVA showed a significant effect of *intensity* ($F_{(2, 36)}$ = 93.34; p < 0.001). The effects of *time* ($F_{(1, 18)}$ = 0.3; p = 0.591), *hemisphere* ($F_{(1, 18)}$ = 0.001; p = 0.971), *group* ($F_{(1, 18)}$ = 1.584; p = 0.224) or any of the interactions were not significant ($0.004 \leq F \leq 2.961$; $0.074 \leq p \leq 0.948$).

SICI (see Fig 4B). A mixed ANOVA revealed a non-significant effect of *hemisphere* ($F_{(1, 18)}$ = 1.377; p = 0.256), non-significant interactions involving the *hemisphere* factor ($0.12 \leq F \leq 2.632$; $0.122 \leq p \leq 0.733$), and a significant *time* x *group* interaction ($F_{(1, 18)}$ = 5.073; p = 0.037; $\eta^2 p = 0.22$). Post-hoc contrasts performed on the estimated marginal means for the combined hemispheres with Bonferroni corrections indicated a significant effect of *time* for the Val66Val group ($M_{Pre} = 34.68 \pm 7.23$; $M_{Post} = 47.85 \pm 6.51$; p = 0.006) but not for the Val66Met group ($M_{Pre} = 46.11 \pm 7.23$; $M_{Post} = 45.9 \pm 6.51$; p = 0.959). Between-subjects comparisons of SICI on time 1 and time 2 showed no significant difference in SICI between the Val66Val and the Val66-Met Pre (p = 0.278) and Post (p = 0.834) motor practice. Further, test MEP amplitudes in the Val66Val ($M_{LH-Pre} = 1.06 \pm 0.13$ mV; $M_{LH-Post} = 1.11 \pm 0.34$ mV; $M_{RH-Pre} = 1.19 \pm 0.19$ mV; $M_{RH-Post} = 1.26 \pm 0.25$ mV) and the Val66Met ($M_{LH-Pre} = 1.05 \pm 0.1$ mV; $M_{LH-Post} = 1.01 \pm 0.21$ mV; $M_{RH-Pre} = 1.19 \pm 0.19$ mV; $M_{RH-Post} = 1.11 \pm 0.2$ mV) groups did not differ before or after
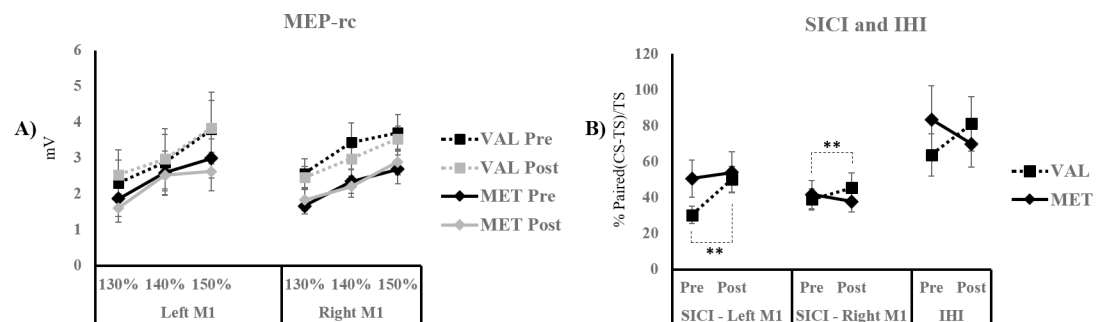


**Fig 4. MEP-rc, SICI, and IHI measures.** MEP-rc (A), SICI (B), and IHI (B) measures Pre- and Post- motor training are shown for the Val66Val Vs. the Vall6Met groups in the Experiment 1. The error bars represent standard errors of the mean. Dashed lines used for comparisons show simple effects. ** p < 0.01.

motor practice ($F_{(1, 18)} = 0.003$; p = 0.960), but they were greater overall in the right M1 compared to the left M1 ($F_{(1, 18)} = 11.139$; p = 0.004). However, test MEP amplitudes did not differ between groups ($F_{(1, 18)} = 1.028$; p = 0.324), and none of the interactions were significant (p ≥ 0.275). Therefore, possible effects of TS MEP intensity on conditioned MEPs in bilateral M1 were equivalent between groups.

IHI (see Fig 4B). A mixed ANOVA revealed non-significant effects of *time* ($F_{(1, 18)} = 0.017$; p = 0.899), *group* ($F_{(1, 18)} = 0.073$; p = 0.791), or *time* x *group* interaction ($F_{(1, 18)} = 1.108$; p = 0.307). Test MEP amplitudes also did not differ before or after motor practice ($F_{(1, 18)} = 1.028$; p = 0.324), nor between groups (Val66Val: $M_{Pre} = 1.05 ± 0.22$ mV; $M_{Post} = 1.2 ± 0.47$ mV; Val66Met: $M_{Pre} = 1.12 ± 0.3$ mV; $M_{Post} = 1.11 ± 0.33$ mV; $F_{(1, 18)} = 0.002$; p = 0.918), and the *time*group* interaction was non-significant ($F_{(1, 18)} = 1.337$; p = 0.263).

**Normality tests.** Normality analyses of the standardized residual distributions using Kolmogorov-Smirnov and Shapiro-Wilks tests revealed significant deviations from normal distribution on several variables. Specifically, TMS data comparisons between the Val66Val and the Val66Met groups were comprised of non-normal distributions in the MEP-rc residuals for the left M1 on the pre- and post- conditions (0.001 ≤ p ≤ 0.002), in the IHI residuals on the pre- condition (p = 0.021), in the RMT residuals on the right M1's post- condition (p = 0.031), and in the 1mV residuals in the left (post- condition; p = 0.032) and right M1 (pre- condition; p = 0.033). Likewise, motor performance comparisons between the Val66Val the Val66Met groups yielded significant standardized residual distribution deviations from normality on condition 2 of the PGS task with the right hand (p = 0.03), on condition 1 of the RT task with the left hand (p = 0.027), and on conditions 1 (p = 0.003) and 2 (p = 0.04) of the PGS task with the left hand. As such, log 10 transformations were computed for all variables and the original analyses were performed with the transformed variables. As a result, there were no changes in the significance of the main effects or interactions reported in the original analyses. Further, non-normal standardized residual distributions of the log 10 variables remained, namely in the MEP-rc residuals in the left (p = 0.037) and right M1 (0.014 ≤ p ≤ 0.033), in the IHI residuals on the post- condition (p = 0.032), and in the 1mV residuals in the left (0.018 ≤ p ≤ 0.046) and right M1 (pre- condition; p = 0.028).

**Intersession reliability.** ICCs were excellent for RMT and MEP-rc measures in the left and right M1 at each intensity level in Val66Val (0.863 ≤ r ≤ 0.978; p ≤ 0.002) and Val66Met groups (0.87 ≤ r ≤ 0.963; p ≤ 0.003). For SICI, ICCs were poor for the left M1 (r = 0.27; p = 0.252) and good (r = 0.677; p = 0.056) for the right M1 in the Val66Val group, and excellent (r = 0.892; p = 0.002) and good (r = 0.673; p = 0.063), respectively, in the Val66Met group. In addition, ICCs for IHI from the left to right M1 were fair and invalid, respectively, for the Val66Val (r = 0.484; p = 0.167) and Val66Met groups (r = -0.192; p = 0.593).

## Experiment 2

**Learning.** In the CR group (see Fig 5A, 5B and 5C), paired-samples t-tests revealed significant speed improvements between R1 and R2 on the RT ($M_{R1} = 216 ± 74.74$; $M_{R2} = 172 ± 60.6$; $t_{(9)} = 3.758$; p = 0.004) and the GPB tasks ($M_{R1} = 21 ± 5.6$; $M_{R2} = 17 ± 4.63$; $t_{(9)} = 4.5$; p = 0.001) but not for the PGS task ($M_{R1} = 0.73 ± 0.24$; $M_{R2} = 0.74 ± 0.26$; $t_{(9)} = -0.09$; p = 0.93).

**TMS.** RMT and 1 mV intensity. Two repeated-measures ANOVAs were used to compare RMT and 1mV intensities before and after motor practice in the CR group's left and right M1 revealed non-significant effects of *hemisphere* ($F_{RMT (1,9)} = 0.596$; p = 0.46; $F_{1mV (1, 9)} = 0.319$; p = 0.586) and *time* ($F_{RMT (1,9)} = 0.396$; p = 0.545; $F_{1mV (1, 9)} = 0.142$; p = 0.715). In addition, the *hemisphere* x *time* interaction was not significant ($F_{RMT (1,9)} = 1.227$; p = 0.297; $F_{1mV (1, 9)} = 0.168$; p = 0.691).
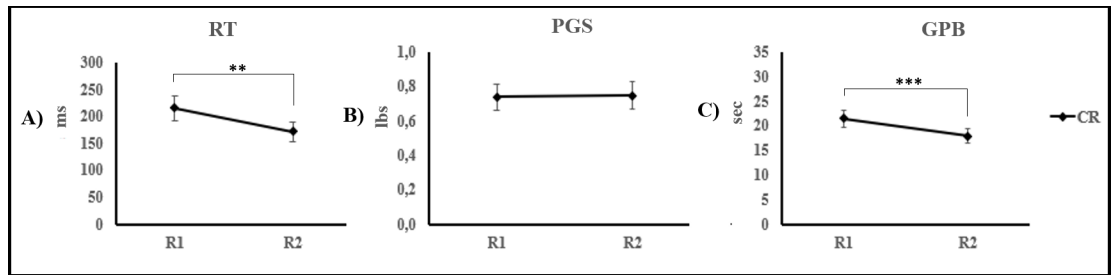
**Fig 5. Motor performances on the rapid tapping (RT), pinch grip strength (PGS), and the grooved pegboard (GPB).** The mean scores on the RT (A), the PGS (B), and the GPB (C) are presented for the CR participants in Experiment 2 on the R1 and R2 conditions with the right hand. The error bars represent standard errors of the mean. Full lines used for comparisons represent main effects. ** p < 0.01; *** p < 0.001.

MEP-rc (see Fig 6A). A repeated-measures ANOVA revealed a significant effect of *intensity* ($F_{(2, 18)} = 46.106$; p < 0.001) and of the *hemisphere* x *time* interaction ($F_{(1, 9)} = 9.361$; p = 0.014). Post-hoc contrasts conducted on the estimated marginal means of the combined intensity levels using Bonferroni corrections revealed a non-significant effect of *hemisphere* before ($M_{LeftM1} = 2.36 \pm 0.39$ mV; $M_{rightM1} = 2.42 \pm 0.35$ mV; p = 0.918) and after motor practice ($M_{LeftM1} = 3.16 \pm 0.49$ mV; $M_{rightM1} = 2.35 \pm 0.36$ mV; p = 0.155), which suggests that the MEP-rc amplitudes did not differ between the left and right M1. However, the within-subjects comparisons showed a significant increase in MEP-rc amplitudes in the left M1 following motor practice with the right hand (p = 0.025) while MEP-rc amplitudes in the right M1 did not differ before and after motor practice (p = 0.541).

SICI (see Fig 6B). A repeated measures ANOVA revealed a significant *time* x *hemisphere* interaction ($F_{(1, 9)} = 5.584$; p = 0.042). Post-hoc analysis showed a significant effect of *time* in the left M1 ($M_{Pre} = 23.05 \pm 4.4$; $M_{Post} = 52.74 \pm 11.13$; p = 0.015) but not in the right M1 ($M_{Pre} = 38.23 \pm 6.35$; $M_{Post} = 46.13 \pm 7.1$; p = 0.351). In addition, within-subjects comparisons showed a significant effect of *hemisphere* pre- motor practice (p = 0.009), whereas SICI did not differ between hemispheres post motor practice (p = 0.367). Test MEP amplitudes did not differ *pre-* or *post-* motor practice ($M_{LH-Pre} = 1.09 \pm 0.15$ mV; $M_{LH-Post} = 0.97 \pm 0.19$ mV; $M_{RH-Pre} = 1.02 \pm 0.21$ mV; $M_{RH-Post} = 1.05 \pm 0.32$ mV; $F_{(1, 9)} = 0.631$; p = 0.447), between hemispheres ($F_{(1, 9)} = 0.007$; p = 0.934), and the *time* * *hemisphere* interaction was not significant ($F_{(1, 9)} = 1.541$; p = 0.246). These results suggest increased SICI before motor practice with the right hand in the left M1 compared to the right M1.
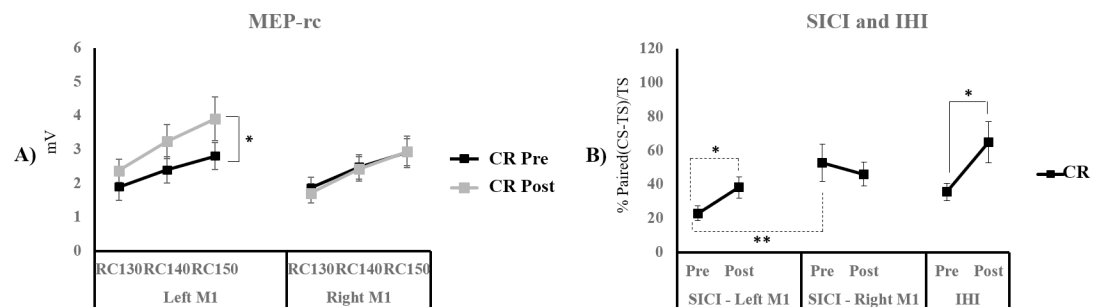


**Fig 6. MEP-rc, SICI and IHI measures.** MEP-rc (A), SICI (B), and IHI (B) measures Pre- and Post- motor training are shown for the CR group in the Experiment 2. The error bars represent standard errors of the mean. Full lines used for comparisons represent main effects and dashed lines show simple effects. * p < 0.05; ** p < 0.01.
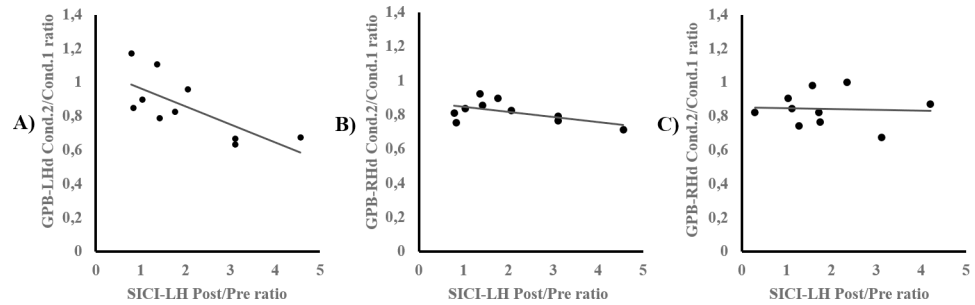
**Fig 7. Correlation analyses between SICI modulation in the left M1 and GPB performance.** Correlations between Post- to Pre- ratio of SICI in the left M1 (abscissa) and condition 2 to condition 1 ratio of GPB performance (ordinate) are displayed for the Val66Val participants' left (A) and right (B) hands, and for the CR group's performance with the right hand (C). Larger SICI ratios indicate a greater decrease in SICI following motor training, and smaller GPB ratios suggest greater improvement from condition 1 to condition 2 on the motor task.

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IHI (see Fig 6B). A paired-samples T-test was used to compare IHI from the left to right M1 and revealed a significant decrease following motor practice with the right hand ($t_{(9)}$ = -2.464; p = 0.036). Test MEP amplitudes did not differ before and after motor practice ($M_{Pre}$ = 1.02 ± 0.15 mV; $M_{Post}$ = 0.98 ± 0.26 mV; $t_{(9)}$ = 0.542; p = 0.601).

## Correlation analyses

See Fig 7A, 7B and 7C. Relationships between SICI variations pre- and post-motor training, and motor performance improvements from condition 1 to condition 2 on the RT and GPB tasks, were assessed using bilateral Spearman tests in the Val66Val and the CR groups. To that end, Post- to Pre- ratios of SICI were computed for the Val66Val and the CR group's left and right M1. Likewise, condition 2 to condition 1 ratios of Val66Val and CR participants' motor performance were performed on the RT and GPB tasks with the right and left hands. In the Val66Val group, Spearman tests revealed non-significant correlations between right M1 SICI ratios and motor improvement ratios on the RT and GPB tasks with the left and right hands (-0.358 ≤ $r_s$ ≤ 0.588; 0.074 ≤ p ≤ 0.855). SICI ratios in the left M1 were significantly correlated to motor improvement on the GPB task with the left hand ($r_s$ = -0.758; p = 0.011), but not with the right hand ($r_s$ = -0.333; p = 0.347), nor with either hands on the RT task (-0.006 ≤ $r_s$ ≤ 0.042; 0.907 ≤ p ≤ 0.987). In the CR group, bilateral Spearman analyses revealed non-significant correlations between condition 2 to condition 1 ratios of motor performance on the RT and GPB tasks with the right hand, and post- to pre-ratios of SICI in the left and right M1 (-0.382 ≤ $r_s$ ≤ 0.406; 0.138 ≤ p ≤ 0.454).

$\displaystyle r_{s}$ rrr

## Discussion

The present results show that Val66Val and Val66Met carriers do not differ on sensorimotor tasks involving speed, precision grip strength, and fine manual dexterity performed with the right or left hand. At the neurophysiological level, Val66Val and Val66Met carriers also did not differ on measures of corticospinal excitability and IHI from the left to right M1. Although SICI did not differ before and after motor practice in the Val66Val and Val66Met groups, Val66Val carriers exhibited a greater decrease in SICI in the bilateral M1 compared to Val66-Met carriers following motor practice with both hands in an alternated sequence. SICI decrease in the Val66Val participants' left M1 was correlated with motor improvement on the GPB task with the left hand. Interestingly, neither groups showed significant modulation of

MEP amplitude or IHI when motor practice with the right hand is immediately preceded and followed by short periods of motor practice with the left hand on the same tasks. These results contrast with the increased MEP amplitudes, decreased SICI in left M1, and reduced IHI from the left to right M1 observed in the CR group, which performed the motor tasks with the right hand only. In addition, while TMS measures vary significantly between subjects, good to excellent test-retest reliability of RMT, MEP, and SICI were demonstrated with sample sizes similar to the present study (10; 10; 12; 15 subjects) [76–80]. This aspect is particularly important considering the main objective of the current experiment was to compare activity-dependent changes in TMS measures before and after motor practice between the Val66Val and the Val66-Met groups. Our results show that the ICC on Pre- Post- RMT and MEP-rc were comparable to those reported in other experiments, as was SICI measured in the Val66Met group's left M1 [76–80]. Other SICI measures were less reliable, particularly in the Val66Val group's left M1 (poor) which is likely due to modulation through motor practice. Thus, the sample sizes were adequate for MEP-rc and SICI comparisons from time 1 (Pre) to time 2 (Post). However, lower reliabilities of the IHI measures may suggest a need for larger samples in future experiments.

The first objective of the present study was to characterize differences in learning and intermanual transfer of sensorimotor skills in Val66Val and Val66Met carriers. At the behavioral level, speed and fine motor dexterity in the left hand improved from condition 1 to condition 2 when no right-hand practice was present between conditions (CL group). These improvements did not differ from those observed in the Val66Val and Val66Met groups. Therefore, improvements in motor speed and fine manual dexterity with the left hand in Val66Val and Val66Met carriers, who performed motor tasks with their right hand for 30 minutes between conditions 1 and 2 with the left hand, are likely attributable to baseline practice with the left hand rather than intermanual transfer from the right to the left hand. Likewise, performance on the PGS task with the left hand did not improve from condition 1 to condition 2, irrespective of group, which again suggests the absence of intermanual transfer from the right dominant hand to the left non-dominant hand. These results contrast with previous studies that reported significant intermanual transfer of precision grip strength, motor speed, and complex fine manual dexterity [63–67, 82]. At the same time, reduced efficacy in intermanual transfer has also been shown with numerous sensorimotor protocols [83–87]. This variability suggests that intermanual transfer of sensorimotor information is a multidimensional mechanism sensitive to the nature of the task, availability of environmental feedback, and training schedule [84, 85, 88–91]. For example, intermanual transfer of sensorimotor information is more effective in tasks with increased reliance on higher-order perceptual and cognitive processes involved in motor planning and anticipation rather than simple dynamics such as force control [84, 85, 89]. Thus, the PGS task used in the present experiment, in the absence of object lifting, would not provide sufficient environmental feedback to foster sensorimotor memory formation, focusing instead on simple dynamic motor control. Indeed, intermanual transfer of simple dynamic motor skills, such as ballistic index finger abductions, relates to the level of effort during repetitive forceful contractions during a single session [48, 50, 55, 92, 93]. In comparison, rapid tapping tasks variants measure maximum contraction speed, which may be defined as inter-tap intervals, instead of maximal force contractions and acceleration [64, 65, 94]. Considering that intermanual transfer of motor speed was observed during intense training on rapid tapping tasks performed over multiple sessions [64, 65], it could be hypothesized that the intermanual transfer of non-forceful dynamic skills may be facilitated by consolidation and retention processes via repeated practice over several days [95]. A similar reasoning could be applied to the fine manual dexterity skills required for the GPB task, as previous experiments demonstrating significant intermanual transfer of complex fine dexterity skills were conducted over multiple sessions spread over several days [67, 96, 97].

Importantly, Val66Met participants did not differ at baseline or following motor practice from their Val66Val counterparts on motor tasks involving fast adaptations of low-force simple dynamic skills. Although replication in future experiments is required, the current results add to the growing body of evidence suggesting that the BDNF Val66Met polymorphism does not interfere with the execution and short-term learning of simple sensorimotor skills with the dominant hand [26–28, 98, 99] while showing similar findings for the left, non-dominant hand. Rather, the BDNF Val66Met polymorphism has been associated with impaired short-term learning and retention of motor skills on more complex tasks such as driving [27]. Hence, the impact of the Val66Met polymorphism on learning and retention of motor skills may be apparent when more complex visuomotor coordination is required, rather than unimanual movements restricted to simple dynamics and kinematics.

The second objective of the present study was to investigate the neurophysiological mechanisms that underlie sensorimotor learning and the intermanual transfer of sensorimotor information from the left to right M1 in Val66Val and Val66Met carriers. In the absence of significant intermanual transfer, motor improvements observed here likely result from practice with each hand separately, independently of practice with the other hand, although repeated practice over several sessions on similar tasks may lead to intermanual transfer [64, 65, 67, 96, 97]. The significant increase in left M1 corticospinal excitability following motor practice reported in Kleim et al. [26] was replicated in the present experiment in the CR group, which performed similar tasks with only their right hand. Consistent with previous studies, the CR group also exhibited reduced SICI in the left M1 and lower IHI from left to right M1 [45, 47, 55, 62]. However, neither Val66Val or Val66Met carriers displayed significant modulation of MEP amplitude in bilateral M1, or IHI from the left to right M1, after practicing with both hands in an alternated sequence. Furthermore, while alternated practice with both hands resulted in reduced SICI in the left and right and M1 of Val66Val carriers, practice with the right hand only did not elicit a decrease in SICI in the right M1. These results suggest that the decrease in SICI in the right M1 of Val66Val carriers is likely associated with the interaction effects of motor practice with both hands.

The discrepancy between neurophysiological activity elicited by practice with the right hand only, and with both hands in an alternated sequence, underlines complex neurophysiological interactions between the two M1s. Indeed, unilateral practice induces transient changes in cortical and corticospinal excitability in the M1 contralateral to the trained hand, as well as in the ipsilateral M1 [49, 53, 55, 56, 100]. These bidirectional interactions between the two M1s are mediated in part by interhemispheric inhibitory mechanisms via transcallosal pathways [52, 57–61]. It has been shown that unimanual practice is associated with decreased IHI from the M1 contralateral to the trained hand to the opposite M1 in procedural skill learning [47], pinch grip tasks [45], and submaximal force contractions over multiple sessions [62]. Moreover, the decrease in IHI correlates with cross education of muscle contractions and non-specific transfer on a procedural motor task [47, 62]. Long-term alterations of IHI have also been associated with extensive bimanual practice, as IHI is significantly reduced in trained musicians compared to non-musicians [101]. Taken together, these observations support the presence of reduced IHI from the trained M1 to the contralateral, untrained M1 following right-hand training found in the CR group. In addition, decreased IHI is associated with reduced SICI in the target M1 following motor training in protocols assessing intermanual transfer [45, 47]. Thus, it could be hypothesized that priming of the right M1 with the left-hand practice before and after training with the right hand facilitated SICI modulation in the right M1 in the Val66Val group. Similar to previous studies on intermanual transfer of motor skills, SICI decrease in the right M1 did not correlate with motor improvements with the contralateral left hand [47, 62], or with right-hand performance on the three tasks. Likewise, SICI

decrease in the left M1 did not correlate with improvements in the contralateral right hand in the CR and Val66Val groups. However, our results showed a correlation between the magnitude of SICI decrease in Val66Val participants' left M1 and increased motor improvement on the GPB task with the ipsilateral left hand. One possible interpretation is that SICI modulation in the left M1 occurring through practice with the right dominant hand is associated with intermanual transfer of low-force sensorimotor skill from the right dominant hand to the left dominant hand, thus underlying a potential role of the dominant M1 in motor skill transfer to the non-dominant M1. Observations of reduced SICI in the ipsilateral M1 during unilateral motor activity could support an association between both mechanisms in the context of inter-manual transfer of motor skill [102, 103]. Future experiments are required to examine this relationship and the underlying mechanisms.

With regards to the absence of MEP amplitude modulation in Val66Val and Val66Met carriers, activation of the right M1 through left hand practice prior to, and after activation of the left M1 with right hand practice, may have interacted with corticospinal excitability levels in the left M1 and its ability to inhibit the opposite M1. For example, simultaneous practice with homologous muscles may decrease, or even suppress, MEP amplitudes in the M1 contralateral to the target hand compared to the unilateral practice condition alone [49], and others have failed to report significant changes in global MEP amplitudes following bimanual motor training [104]. The presence of an inhibitory interaction is further supported by reports of increased MEP amplitudes in the M1 contralateral to the trained hand on similar tasks in Val66Val carriers [26, 27]. As for the absence of IHI modulation in participants who performed the tasks with both hands, the available data clearly supports communication between M1s during unilateral motor tasks, as unilateral practice reduces IHI in both directions with adjusted CS intensities while either hand is active [59, 105, 106]. Likewise, rTMS to the left M1 reduces IHI in both directions, and IHI may be reduced or facilitated bidirectionally, or simultaneously enhanced in one direction and reduced in the other following transcranial direct current stimulation [106, 107]. Therefore, the execution of tasks with both hands in sequence could have triggered complex interactions in IHI resulting in the suppression of IHI from the left M1 to the right to M1.

Importantly, the present results show that the BDNF Val66Met polymorphism is associated with altered activity-dependent modulation of SICI in bilateral M1. It is also worth noting that the reported difference in SICI modulation between Val66Val and Val66Met carriers is not due to RMT or 1mV intensities because neither differed between groups, before or after motor training. These results are not surprising considering that BDNF regulates GABA-inhibitory synapse formation and maturation [16, 108–112]. For example, sensory deprivation leads to delayed GABA-ergic cell maturation in wild type mice, but not in BDNF over-expressing mice [108], and BDNF over-expression induces early maturation of GABA-ergic innervation and inhibition [109]. In the short-term, the BDNF and its precursor, pro-BDNF, modulate GABA-ergic synaptic plasticity, including presynaptic GABA release, and LTD presumably through NDMA-dependent transmission [9, 15, 16, 110, 111, 113, 114]. An underlying mechanism of fast changes in inhibitory transmission involves GABA-A receptor phosphorylation regulation associated with BDNF [5]. Moreover, sustained exposure to glutamatergic transmission and BDNF enhances long-lasting potentiation of GABA-A receptor related synaptic activity, which incidentally mediates SICI in the motor cortex [42, 110, 115, 116]. As such, the effects of the BDNF Val66Met polymorphism on cortical excitability have been extensively studied with TMS or tDCS plasticity-inducing protocols (see review by Chaied et al., 2014 [117]). Though the results have been inconsistent, the available data tend to confirm the association between altered cortical plasticity and the Val66Met polymorphism [117]. Specifically, GABA-A mediated SICI in the motor cortex was elevated at baseline, and following cathodal tDCS, in healthy

Val66Met carriers compared to their Val66Val counterparts [118, 119]. Thus, the present results support the idea that BDNF Val66Met polymorphism is associated with altered short-term activity-dependent cortical excitability mechanisms in bilateral M1, despite the absence of differences in short-term motor learning of low force simple dynamic skills compared to Val66Val carriers. However, because SICI is associated with motor learning and intermanual transfer of procedural skill [39, 45–47], the absence of activity-dependant modulation of SICI provides additional support for the short-term learning and retention problems on more complex tasks [27, 68], as well as impaired intermanual transfer of procedural skill reported in Val66Met carriers [29].

## Limits

Non-normal distributions are probably due to artefacts related to the small sample sizes used in the current study, which was determined *a priori* based on previous studies on the associations between the Val66Met genotype, cortical plasticity, and motor learning (7, 8, 11, and 12 Val66Met subjects) [26–28, 120]. Notably, the analyses comprised of non-normal transformed variables did not conclude to significant main effects or interactions. While simulation studies with ANOVA tests have shown that the false positive rate is not much affected by the violation of the assumption of normal distribution [121], there is also a possibility of an overestimation of type 2 errors under such conditions [122]. Therefore, the negative results in this study have been interpreted with care, not by suggesting the absence of effects in the general population but rather by highlighting similarities with the existing literature. Importantly, the standardized residuals distribution of the variables involved in the SICI analysis comparing the Val66-Val and the Val66Met participants did not differ from normal distribution. Therefore, the validity of this study's main finding, namely, the differential activity-dependent modulation of bi-hemispheric SICI between the Val66Val and the Val66Met participants, is supported. Nevertheless, replication in future experiments is required.

## Supporting information

**S1 Minimal Data Set.**
(XLSX)

## Author Contributions

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**Validation:** Olivier Morin-Moncet, Hugo Theoret.

**Visualization:** Olivier Morin-Moncet.

**Writing – original draft:** Olivier Morin-Moncet.

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