Is Bimanual Interference Affected in the Case of a Central Proprioceptive Loss? New Insight From a Left-Brain-Damaged Single-Case Study

Neuropsychology

Is bimanual interference affected in the case of a central proprioceptive loss? New insight from a left brain damaged single-case study.

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Full Title:	Is bimanual interference affected in the case of a central proprioceptive loss? New insight from a left brain damaged single-case study.
Article Type:	Case Study
Abstract:	Objective. It was suggested that the bimanual coupling effect might be linked to motor intentionality and planning. However, previous results in pathological and healthy individuals seem to underline also the pivotal role of bottom-up sensori-motor information. Methods. In this single-case study, the Circles-Lines Coupling Task was administered to a left parietal brain damaged individual. he brain lesion caused a central proprioceptive loss relative to the impaired right hand, when out of the visual control. We sought to investigate whether the movement of the unaffected hand induced an efficient coupling effect on the movement of the affected one. The task was performed in the presence and absence of visual input. The patient's performance was compared with healthy controls. Results. We observed the traditional bimanual coupling effect in healthy controls. Moreover, we also replicated the effect when they performed the task blindfolded. In the case of the patient, both hands showed the typical ovalization of the line trajectory when the task was performed in visual modality. Interestingly, when the patient performed the task blindfolded, the trajectories of the impaired right hand seemed to be uninfluenced by the concomitant circular movement of the spared left hand. Conclusions . The movement of the unaffected hand can induce a bimanual coupling effect on the movement of the affected one, only when the visual input is available. In absence of a visual feedback, the aberrant proprioceptive information might preclude the emerging of bimanual coupling, even in the case of a preserved motor intentionality and planning.
Keywords:	left-brain damage patient; central proprioception; intermanual coordination; single-case study; vision
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Response to Reviewers:	

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2019, 26th November

Editor

Keith O. Yeates, Ph.D.

Neuropsychology

Dear Editor,

Please find enclosed the second revised version of our manuscript titled "**Is bimanual interference affected in the case of a central proprioceptive loss? New insight from a left brain damaged single case study.**" by Scarpina Federica, Tagini Sofia, Rabuffetti Marco, Albani Giovanni, Garbarini Francesca, Mauro Alessandro.

Once again, we would like to thank you and the Reviewers for the comments on our manuscript. We are glad to read that you and Reviewers were satisfied with the new version of our manuscript as well as that our work was so appreciate.

Following the Reviewer 3's suggestions, we put all our efforts in providing a new version of our manuscript that might free from typos and inconsistencies. Moreover, we clarified the figures' captions and we provided a new figure 4, that is now consistent with the other figures.

We provided a point-to-point answer to the Reviewers. Moreover, we underlined all the changes made in our manuscript.

Yours sincerely,

On behalf of the Authors,

Federica Scarpina

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Title: Is bimanual interference affected in the case of a central proprioceptive loss? New insight from a left brain damaged single-case study.

Rebuttal Letter

Reviewer #1

REPLY. Once again, ee would like to thank the Reviewer for his/her comments to our manuscript.

Reviewer #2:

All my comments have been adequately addressed.

REPLY. We would like to thank the Reviewer for his/her comments to our manuscript.

Reviewer #3:

Overall the authors have done a good job addressing my previous concerns. I only have some minor comments regarding the clarity of their writing in certain sections as well as improvements that could be made regarding the Figures.

REPLY. We thank the Reviewer for his/her comments to our manuscript. In the new revised version, we provided clearer figures captions as well as we provided a new Figure 4, in which data were shown with the same order of the other figures (left: controls; right: patient). Also, thanks to the comments, we amended some criticisms in our writing.

General comment: While I appreciate the work the authors have done revising the manuscript, there are still a number of typos and awkward phrases that will need to be cleaned up before it is published. Perhaps this could be taken care of at the copy editing stage.

REPLY. We really thank the Reviewer for his/her kindness in signaling us typos and inconsistencies in our manuscript. We checked it again; in yellow we underlined changes.

1. On page 12 when you are describing the results for the no-vision condition vs. controls you note that, "the difference between the congruent and the incongruent index relative to the patient's performance was NOT different from controls [$t(15) = 3.88$; $p = 0.001$; effect size = 4.179 (95% CI = 2.66 to 5.9)]" Don't you mean to say that it WAS different from controls? The statistics presented seem to indicate that it was different for the right hand. This is the most important findings form the study, so it is important to be clear about this.

REPLY. We really thank the Reviewer to have noticed this typo. We changed the sentence.

Pag. 12. *About the right hand, the difference between the congruent and the incongruent index relative to the patient's performance was significantly different from healthy participants' performance [t(15) = 3.88; p = 0.001; effect size = 4.179 (95% CI = 2.66 to 5.9)]. Specifically, the OI was larger in the incongruent condition than the congruent condition for controls as expected. However, this pattern was not observed in the patient's performance. Thus, when the visual feedback was precluded, the normal movement of the intact hand did not induce a coupling effect on the movement of the affected one.*

2. Also, in the very next line you state that, "Specifically, in the control condition, the OI was larger in the incongruent condition than the congruent condition for controls as expected." What "control condition" are you referring to here? Do you simply mean that, for controls, the OI was larger in the incongruent condition compared to the congruent condition?

REPLY. We really thank the Reviewer to have noticed this typo. We changed the sentence. Please, refer to the previous comment (#1).

3. At the beginning of the Discussion on page 15 you state that, "The single-case patient presented in this paper suffered of a conscious loss of proprioceptive information relative to the right hand when out of the visual control, consequently to a left-brain damage." You might want to reword this sentence and be more specific about the regions that were damaged in your patient as the "left brain damage" is quite vague.

REPLY. Following this suggestion, we changed the sentence.

Pag. 15: *The single-case patient presented in this paper suffered of a conscious loss of proprioceptive information relative to the right hand when out of the visual control, consequently to a left brain damage involving the postcentral gyrus and the superior parietal gyrus.*

4. Bottom of page 16, "thus, the interference effect did not arise (Figure 4, right panels)." You should probably reference Figure 5 here as this is where the data is located to back up this statement. Furthermore, the "right panels" of Figure 4 are referring to the control data, not the patient data.

REPLY. We really thank the Reviewer for having noticed this inconsistency. We corrected it. Moreover, in order to be consistent through our figures, we reported a new version of the Figure 4, where the patient's performance was shown on the right panel, and the controls' performance on the left panel.

5. The final sentence of the paper, "….the role of primary sensory information might not be of less importance in promoting limbs' interactions," is confusing and does not clearly state the main finding from the paper. Be clear about why your results are important, e.g., "The current study demonstrates that proprioceptive information makes an important contribution to the bimanual coupling effect" or something along those lines.

REPLY. We thank the Reviewer for his/her suggestion. We changed the sentence as follow.

Pag. 16 *Besides any possible interpretations of our findings, and the limited generalizability of our results, the current case-report study demonstrated that central proprioceptive information contributes importantly to the bimanual spatial coupling effect.*

Figures:

1. The units are not clearly stated in the captions for Figures 3 and 5.

REPLY. We agree with the Reviewer that the units were not expressed in the captions, as in line with other published papers (Garbarini et al., 2012, 2013, 2014, 2015ab). This happened because OI was computed according to the formula expressed in the manuscript. In different way, we reported the unit (that was mm) in the caption relative to the Figure 4, in which the row drawings were shown. we wrote again the captions of the Figure 3 and 5 to clarify some points.

Figure 3. Bimanual Coupling Task - vision condition. ***Left panel:*** *About the healthy controls' performance, the Ovalization index (OI) mean (vertical bars) and the standard error (horizontal lines) for the congruent index and the incongruent index, relative to the right hand (upper part) and the left hand (below part) were reported. Specifically, the congruent index was computed as the difference between the mean of the OI registered in the congruent bimanual trials and the mean of OI relative to the unimanual trials; for the incongruent index, the mean of the OI registered in the incongruent bimanual trials was subtracted from the mean of OI relative to the unimanual trials.* ***Right panel:*** *about the patient's performance, the mean OI (horizontal bars) for the congruent index and the incongruent index, relative to the right hand (upper part) and the left hand (below part), was reported. The p-value was shown; a value higher than 0.05 (not significant) indicated that the difference between the two indexes about the patient's performance did not differ compared with the difference registered for the controls. Patient and controls reported a similar performance: the OI reported in the congruent index was lower compared with incongruent index, in line with the expected effect.*

Figure 5. Bimanual Coupling Task – no vision condition. ***Left panels:*** *about the healthy controls' performance, the Ovalization index (OI) mean (vertical bars) and the standard error (horizontal lines) for the congruent index and the incongruent index, split for the right hand (upper part) and the left hand (below part) were reported. Specifically, the congruent index was computed as the difference between the mean of the OI in mm registered in the congruent bimanual trials and the mean of OI relative to the unimanual trials; for the incongruent index, the mean of the OI registered in the incongruent bimanual trials was subtracted from the mean of OI relative to the unimanual trials.* ***Right panels:*** *about patient's performance, the mean OI (vertical bars) for the congruent index and the incongruent index, split for the right hand (upper part) and the left hand (below part) was reported. The p-value was shown; a value higher than 0.05 (not significant) suggested that the difference between the two indexes registered about the patient's performance did not differ respect compared with the controls' performance; in other words, patient and controls reported a similar behaviour. Instead, if the value was lower than 0.05 (significant, in bold), it indicated that such a difference was not comparable between patient and controls: this was the case of the patient's performance for the right hand. The difference between the patient's OI relative to the congruent condition and the incongruent condition indexes registered about the right hand was significantly different when compared with the controls, who reported the expected pattern (i.e. the congruent index was significantly lower than the incongruent index).*

2. Add a note to the caption in Figure 4 drawing the reader's attention to the right hand-no vision condition for the patient where there is an absence of ovalization (i.e., absence of coupling) which is the main findings from the paper.

REPLY. We thank the Reviewer for this very useful suggestion. We wrote again the caption relative to the Figure 4.

Examples of the patient's (right panel) and a healthy participant's (left panel) for the line trajectories of the right hand and the left hand in the incongruent bimanual condition (i.e. when participant drew lines with one hand, and circles with the other) were showed relative to the vision condition (upper part) and no vision condition (below part). Lat.-coord. = the horizontal displacement in mm; up-down coord = vertical displacement in mm. For each picture, we reported the OI). Thus, it might be noticed that in the no vision condition, the patient's trajectory relative to the right hand was clearly less ovalized (i.e. less displaced on the horizontal axys) in comparison with the control: this suggested the absence of bimanual coupling. Such a difference was not reported in the other conditions, in which instead bimanual coupling emerged.

3. In the caption for Figure 5 there is a typo when referring to the right panels, "about patient's performance, the mean OI (vertical bars) for both index and incongruent index…" I think you need to specify for, " both the congruent index and incongruent index.."
Also, in the same figure caption, for the last sentence (referring to the difference between the patient and controls) you need to make it clear that this was specifically for the right hand.

REPLY. We thank the Reviewer for this suggestion. Please, refer to the previous comment (minor comment section, #1) to verify our new caption for the Figure 5.

4. For Figures 3 and 5 it might simplify things if you put the data for the controls and the patient on the same graph as it would make visual comparisons easier.

REPLY. We decided to separate the data relative to the controls and the patient since we performed multiple analyses, which results might be complex to be shown in a single graph. However, we carefully set the same range in the y-axys.

Is bimanual interference affected in case of central proprioceptive loss? New insight from a left brain damaged single case study.

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Title: Is bimanual interference affected in the case of a central proprioceptive loss? New insight from a left brain damaged single-case study.

Abstract

Objective. It was suggested that the *bimanual coupling effect* might be linked to motor intentionality and planning, that are the top-down components of motor execution. However, previous results in pathological and healthy individuals underlined also the pivotal role of bottom-up sensori-motor information.

Methods. In this single-case study, the Circles-Lines Coupling Task was administered to a left parietal brain damaged individual. The cerebral lesion caused a central proprioceptive loss relative to the impaired right hand, when out of the visual control. For the first time in literature, we sought to investigate whether the movement of the unaffected hand induced an efficient coupling effect on the movement of the affected one. The bimanual task was performed in the presence and absence of visual input. The patient's performance was compared with healthy controls.

Results. We observed the traditional bimanual coupling effect in healthy controls. Moreover, we also replicated the effect when they performed the task blindfolded. In the case of the patient, both hands showed the typical ovalization of the line trajectory when the task was performed in visual modality. Interestingly, when the patient performed the task blindfolded, the trajectories of the impaired right hand seemed to be not influenced by the concomitant circular movement of the spared left hand.

Conclusions. The movement of the unaffected hand induced a bimanual coupling effect on the movement of the affected one, only when the visual input was available. In absence of a visual feedback, the aberrant proprioceptive information might preclude the emerging of bimanual coupling, even in the case of a preserved motor intentionality and planning.

Keywords: left-brain damage patient; central proprioception; intermanual coordination; single-case study; vision

Public Significance Statements.

When individuals simultaneously trace out lines with one hand and circles with the other, the two hands influence each other. This phenomenon, noted as bimanual coupling effect, is linked to the motor intentionality and planning.

Here we studied this behaviour in a brain damaged individual who experienced a central proprioceptive loss relative to the impaired right hand, when out of the visual control.

In absence of a visual feedback, the aberrant proprioceptive information might preclude the emerging of bimanual coupling, even in the case of a preserved motor intentionality and planning.

Introduction

During our everyday life, we often encounter several situations in which we rely on both hands to interact properly and efficiently with the environment. This ability, called *bimanual coordination*, is the natural propensity of primates (Kermadi, et al., 1998; Kazennikov, et al., 1999) and humans (Franz, 1997) to coordinate and synchronize limb movements. This behaviour is so natural that people tend to perform symmetrical movements, even when the situation explicitly requires them to move their limbs asymmetrically (Carson et al., 1997). In other words, in the case of incongruous but simultaneous movements, limbs interfere reciprocally (Cattaert et al., 1999; Heuer, 1993; Marteniuk and MacKenzie, 1980). For instance, while individuals draw lines with one hand and circles with the other, the movement trajectory of both hands assumes an oval shape, as a consequence of their reciprocal interference (Franz et al., 1991). This behaviour is called *bimanual coupling effect*.

Given the adaptive value of bimanual coordination, this phenomenon has been largely investigated in healthy individuals as well as in clinical populations. Nevertheless, it is still a matter of debate whether an intact cognitive representation of an action is sufficient for the bimanual coordination, or if peripheral sensory information also plays a significant role. The Intermanual Cross-talk Model (Marteniuk and MacKenzie, 1980) supports the first stance. According to this model, bimanual coordination is driven by the mutual integration of the two limbs' motor plans; if the motor plans differ, their interaction results in a reciprocal assimilation (Cattaert et al., 1999; Heuer, 1993; Marteniuk and MacKenzie, 1980). Two neural pathways have been proposed to underpin intermanual cross-talk. The first pathway is represented by the uncrossed fibers of the lateral corticospinal tract (Gray et al., 2016). Indeed, despite each arm is mainly controlled by the contralateral cerebral hemisphere, it also receives a little amount of input from the ipsilateral hemisphere (Cattaert et al., 1999) relative to the other limb's motor plan. The other pathway of intermanual cross-talk is via the corpus callosum (Carson, 2005; Swinnen and Gooijers, 2015), which mediates the interhemispheric communication. Furthermore, the corpus callosum - together with other cerebral areas, such as the inferior parietal and premotor cortices, as well as the ventral visual pathway – plays a crucial role for the limbs' spatial interference, and specifically for the selection and planning of a motor response (Ivry et al., 2004). Indeed, patients with corpus callosotomy do not show bimanual interference and reciprocal assimilation of asynchronous incongruent movements (Franz et al., 1996; on the role of the maturation of callosal connections in bimanual coupling see Piedimonte et al., 2014). The central role of motor planning in bimanual coordination is also supported by behavioral studies involving neurological populations (Franz and

Ramachandran, 1998; Garbarini et al., 2012, 2013, 2014; 2015a). According to Garbarini & Pia, 2013, an intact representation of motor planning and intentionality enhances bimanual coupling effect, independently from limb movements and on-line sensory feedback (such as the peripheral or central proprioceptive processing). As reported in previous studies (Garbarini et al., 2012, 2013, 2015a), in which brain damaged hemiplegic individuals imagined to perform incongruent movements with the paretic limb together to actual movements of the spared limb, they show an appropriate coupling effect with the unimpaired limb, despite the absence of sensory-motor feedback from the affected limb. Similar results have been reported in healthy participants when they draw lines with their right hand, while they imagined to perform incongruent movements with the left hand, that was immobilized (Garbarini et al., 2015b). Overall, these studies support the hypothesis that intact action representation and motor intentionality play a central role in bimanual interference, in line with the Intermanual Cross-talk Model (Marteniuk and MacKenzie, 1980).

However, proprioceptive information might contribute to coordinate simultaneous movements. Indeed, deafferentiated patients show poor coordination abilities in reaching movements, (Jackson et al., 2000), as well as in spatially (Spencer, 2005) and temporally (Drewing et al., 2004) synchronized bimanual actions. Moreover, in healthy individuals, when peripheral proprioceptive sensations from the limbs are experimentally altered (for example through a vibration applied to the tendons), the ability to perform simultaneous congruent and incongruent circular movements becomes less efficient (Serrien et al., 1995; Verschueren et al., 1999). Thus, whether bimanual coordination is primarily driven by top-down (i.e. cognitive motor representations) or bottom-up processes (sensory-motor input) is still an open question.

In the present study, we described the single-case of a left-brain damaged patient, who reported an impaired proprioceptive processing of the controlesional right arm, in absence of any motor disorder. Since the proprioceptive impairment was due to a lesion of the central nervous system, this patient showed an aberrant central proprioceptive processing (see Fossataro et al., 2018 for a different single-case of right-brain damaged patient who showed difficulties in central proprioceptive processing, with spared left arm movement, after right brain lesion). No impairment in motor awareness (i.e. anosognosia) or body delusion (such as asomatognosia or somatoparaphrenia) relative to the affected limb was observed, as well as no unilateral neglect relative to the personal and peripersonal controlesional space. The absence of these symptoms and signs was in line with the fact that the cerebral lesion regarded the left cerebral hemisphere. On the contrary, in previous studies right brain damaged patients were studied (Garbarini et al., 2012, 2013, 2015a; Fossataro et al., 2018). Interestingly, our patient did not show any sign of paresis:

she/he moved the controlesional limb. Thus, we were able to assess the performance of both the affected hand and the unimpaired hand in a bimanual coupling task, unlike the previous studies (Garbarini et al., 2012, 2013, 2015a) in which only one arm was assessed. To study the bimanual coupling effect, we adopted the Circles-Lines Coupling Task (Garbarini et al., 2012, 2013, 2014, 2015ab, Piedimonte et al., 2018; Della Gatta et al., 2017; Burin et al., 2019): in this common spatial task, when participants draw simultaneously incongruent shapes (i.e. a line and a circle), the line drawing generally assumes an oval/curved shape. Crucially, this effect is not detectable in the unimanual (only one hand drawing lines) and in the congruent bimanual (both hands drawing lines) movements. Thus, the line ovalization (represented by the *ovalization index*) represents a significant evidence of the spatial bimanual interference. According to several previous studies (Garbarini et al., 2012, 2013, 2014, 2015ab; Piedimonte et al., 2014, 2018; Della Gatta et al., 2017; Burin et al., 2019), here we focused on the line drawing, comparing the patient's performance with healthy participants, in order to verify whether the bimanual interference emerged. The task was performed in presence and in absence of visual information, since the patient reported a central proprioceptive loss when the affected limb was out of her visual field. Thus, we were able to report preliminary experimental evidence about the role of vision on bimanual coordination.

In this study, we sought to provide evidence about the consequences of a central proprioceptive loss on bimanual coordination, when motor action and motor awareness were spared. In the literature, previous studies involving healthy individuals showed that bimanual interference is not modulated by the experimental alteration of an afferent sensory feedback: thus, spatial interference might primarily emerge at the efferent level of motor planning and intentionality (Swinnen et al., 2004, de Boer, et al., 2013; Dounskaia et al., 2010; Ridderikhoff et al., 2005; Spencer et al., 2005; Garbarini et al., 2015a). Accordingly, when we focused on the effect of the affected hand on the intact one, in our patient we should expect a bimanual coupling effect comparable to healthy controls, despite the impaired central proprioceptive feedback of the affected hand. The previous studies mainly focused on the interference effect of the manipulated hand (where afferent source of information was altered) on the normal (not manipulated) hand. On the contrary, in the present study, we investigated how the concurrent movement of the intact hand might affect the trajectories of the impaired hand. As previously stated, there is no previous study in which the effect of the pathological hand movements on the spared hand was investigated in the Circles-Lines Coupling Task (Garbarini et al., 2012, 2013). Thus, this manuscript would provide the first preliminary experimental answer to the following question: did the movements of the unaffected hand induce a coupling effect on the movements of the affected one?

Methods

The present study was performed in accordance with the ethical standards laid down in the Declaration of Helsinki. It was approved by the Ethical Committee of the involved Institute. All participants provided a written informed consent.

Case description.

The patient was a right-handed individual, whose age was in the range of 50-55 years. The patient was admitted to the Department of Neurology and Neurorehabilitation of the involved Institute. In June 2015, the patient complained of paresthesia on the right part of the body. This symptom was confirmed by a neurological examination. Moreover, a mild strength deficit in right upper and lower limbs was recognized, in absence of other pathological signs. The MRI examination revealed a meningioma in the parietal cortex of the left hemisphere. The meningioma was removed by neurosurgery in another medical center. Levericetam was used to prevent seizures and steroids to reduce oedema of perisurgical regions. After the surgery, the patient reported two episodes in which she/he did not recognize and misidentify her/his relatives for a short period of time (about 10 seconds), until someone touched his/her upper right limb. The clinicians concluded that these events were due to focal seizures, in line with the registration of peak-wave EEG alterations. Thus, the Levetiracetam daily dosage was incremented. After the surgery, the patient also complained of episodes of altered awareness of the right upper limb position. Sometimes she/he noticed her/his right arm in a different position with respect to where she/he believed it should be, as if the right arm moved out of his/her conscious control. Moreover, the patient experienced difficulty in locating his/her arm's position when the limb was out of vision (when the arm was covered by the bed sheet). These symptoms persisted at the time of the present study (March, 2016). The neurological examination, performed at the time of the experiment, indicated mild multidirectional sways of the trunk during the up-right posture, and of the right upper and lower limbs during the Mingazzini's test; a mild loss of muscular strength of the right limbs; a dysmetric response of both limbs (predominantly on the right side) during the finger-nose test when performed with eyes closed; a moderate alteration of tactile and pain sensation on the right bodily side. The neurological examination excluded peripheral neuropathy: the osteotendineous reflex and the muscular trophism was normal in all limbs. In order to confirm the central origin of the mild reduction in muscular strength and of paresthesias in the right upper and lower limbs, a nerve conduction study and a electromyographic study were performed, the results of which fell within the range of normality.

The Magnetic Resonance Imaging study, which was performed at the time of the experiment for clinical purposes, showed the outcome of the meningioma removal surgery characterized by leukomalacia and gliosis in both the postcentral gyrus and the superior parietal gyrus in the left cerebral hemisphere (Figure 1).

[Figure 1 around here]

At the time of the experiment, a complete neuropsychological quantitative assessment was performed by an expert neuropsychologist, in line with the standard procedure of the involved Institute. The neuropsychological tests for each assessed cognitive domain as well as their results were reported in Table 1. Moreover, a qualitative assessment of pantomimed tool-related (to test ideational apraxia) and gesture (to test ideomotor apraxia) performance was performed (De Renzi et al., 1980; Buxbaum and Randerath, 2018); both hands were tested. He/she showed no difficulty, in line with the absence of patient's and relatives' reports of complains in daily activities; the patient was completely self-sufficient in the all activities of daily living, according to the nursing records. The neuropsychologist concluded for the presence of moderate reduction in ideomotor speed, in absence of any significant cognitive difficulties or any sign of dementia.

[Table 1 around here]

Control group. Sixteen right-handed healthy individuals (4 males; *Age* in years M = 41; DS = 13; *Education* in years M = 16; SD = 2) were enrolled as controls for the experiment. According to the Crawford & Garthwaite (2005)'s method, the patient's age was not significantly different from the control group's mean [$t(15) = 0.74$; $p = 0.46$; effect size = 0.76 (95% CI = 0.19 to -1.32)].

The bimanual coupling task. An adapted version of the Circles-Lines Coupling Task (Garbarini et al., 2012, 2013, 2014, 2015ab; Piedimonte et al., 2018; Della Gatta et al., 2017; Burin et al., 2019), was used in this study. Each participant was seated in front of a table on which two graphics tablets (Bamboo Pen & Touch, Wacom Co., Ltd., Vancouver, WA, USA) laid, positioned one to the right and one to the left of the participant's sagittal midline (Figure 2, right part). The size of the tablets' active area was 155 × 95 mm. The tablet area was replicated on a laptop PC (Windows 7 and Windows 10 were both used on considered PCs). The pen tracing was measured at a sampling rate of 100 Hz and with a spatial resolution of 0.1 mm.

[Figure 2 around here].

Participants were asked to perform unimanual or bimanual movements in different conditions: they drew continuously vertical lines and/or circles for 12 seconds in each trial. The inter-trial interval was 6 seconds long. Participants started and stopped the movement according to verbal instructions provided by the experimenter. The experimental conditions were: *i) unimanual*, in which participants drew lines only with one (left or right) hand, while the other hand was in resting position; *ii) congruent bimanual*, in which participants drew contemporary lines with both hands; *iii) incongruent bimanual*, in which participants drew lines with one hand and circles with the other. For each condition, the participants performed 10 trials, for a total of 50 repetitions (1. unimanual with the right hand; 2. unimanual with the left hand; 3. congruent bimanual with both hands; 4. incongruent bimanual: lines with the right hand and circles with the left hand; 5. incongruent bimanual: lines with the left hand and circles with the right hand). Participants were instructed to perform self-paced movements. No specific request about size or velocity was provided, neither no example of the circle or of the line was showed (Figure 2, left part). The movement trajectories of the line drawings were automatically recorded by the two tablets. Trials were presented in pseudorandom order (no more than 3 consecutive trials of the same experimental condition). The task was executed twice, with and without visual information (i.e. participants were blindfolded). The patient executed first the vision condition, and secondly the no vision condition; instead, the order of conditions was counterbalanced for the control group.

Drawing analyses.

For each trial, the raw recording consisted of the measured trajectory of the pen point (x = tablet lateral coordinates; y = tablet vertical coordinates) over successive up-and-down cycles.

This drawing trajectory differed from the ideal one, i.e. a continuous up-and-down exclusive vertical displacement, because of the presence of a lateral component. This component basically results from four main sources: *i)* a real ovalization component, in which the lateral displacement during up-tracing must be fairly equal in magnitude and contrary in sign with lateral displacement during down-tracing); *ii)* a slow wandering drift, in which the lateral displacements during up- and down-tracing has the same sign throughout several cycles); *iii)* the crosstalk of the vertical tracing direction when it is inclined relative the vertical tablet axis, and *iv)* a random stocastic component due to motor control inaccuracy. In order to focus on the line ovalization, i.e. the phenomenon related to bimanual coupling, we adopted specific algorithms to discard the components unrelated to the ovalization, that were: drift, vertical crosstalk and random lateral components (Garbarini, 2012). The main direction of the raw pen point trajectory was identified as the vertical direction and the related coordinate transformation applied to align the up-down drawing direction with the y-axis

(and consequently the perpendicular horizontal direction aligned with x-axis). A slow lateral drifting of the pent point trajectory (occurring especially in the blindfolded condition) was identified with an overall 8-th grade polynomial curve and removed as an offset (Garbarini et al., 2012).

The detrended and realigned tracing trajectory was segmented, in the time domain, in single cycles by identifying its apical points. It allowed us to compute, on each i-th tracing cycle, the variable:

$$oi_i = stdev(x_i)/stdev(y_i)$$

Finally, the *ovalization index* (OI) was defined (Garbarini et al., 2012) as the mean value of the cycle-related time-series, according to the following formula

$$OI = 100 * \sum_{i=1}^{N} oi_i \Big/ N$$

Specifically, OI value was zero for straight tracing trajectories, and it showed increasing values for increasing ovalization up to 100, which represented perfect circular tracing trajectories.

The OI generally stabilizes after 4/5 cycles. Thus, a higher number of cycles should not significantly change the OI (Garbarini et al., 2012). Consequently, in our study, the OI was not affected by the number of performed cycles, as well as by the drawing size (the index was a ratio) (Garbarini et al., 2012).

Finally, in addition to the traditional OI (Garbarini et al., 2012, 2013, 2014, 2015ab; Piedimonte et al., 2018; Della Gatta et al., 2017; Burin et al., 2019), we computed the standard deviation of the *vertical component of the drawing trajectory* (S), expressed in mm: it was relative to the vertical extension of the drawing (since 99% of values from a normal distribution lie in an interval spanning 6 times the distribution standard deviation). Finally, we computed the *average drawing velocity* (V) expressed in mm/s.

Statistical analyses.

About the OI, for each participant we computed two indices (Garbarini et al. 2016) for the experimental conditions (with and without visual feedback) for each hand independently:

- *congruent index:* the mean of the OI registered in the trials relative to the *congruent bimanual* condition was subtracted from the mean of OI relative to the *unimanual* trials, independently for the right hand and the left hand;

- *incongruent index*: the mean of the OI registered in the *incongruent bimanual* trials was subtracted from the mean of OI relative to the *unimanual* trials, independently for the right hand and the left hand.

In the controls and in the patient, we considered outliers any value out of the two SD from the subject's mean; these scores were not entered in the successive analyses.

In the statistical model, we studied right and left hands independently. Preliminary, we verified the presence of the coupling effect in the control group, through a repeated-measures ANOVA with the within-factors of *Condition* (vision *vs* no vision) and *Index* (congruent *vs* incongruent). A priori, we might expect a significant main effect of *Index*, suggesting the presence of the bimanual coupling interference (i.e., higher OI) in the incongruent condition. As regards the role of vision on the performance, the absence of a main effect of *Condition* would suggest that the presence of a visual input did not affect the bimanual coupling interference. Successively, we investigated the difference between the patient's performance in opposition to the controls. To this aim, we used the Revised Standardized Difference Test (Crawford & Garthwaite, 2005; Crawford, et al., 2010): as standard practice, this method is adopted in neuropsychological single-case studies, when one individual's performance is compared with a small control sample, as done in the present article. Specifically, this procedure allowed us to verify whether the difference between the patient's congruent and incongruent indexes was significantly different from the difference between the same conditions (again, the congruent and the incongruent indexes) in the control sample. When the p value was higher than the threshold of 0.05 (i.e., not significant), the patient's difference between the two indexes was similar to controls. On the contrary, in case of a significant p value (i.e. ≤ 0.05), the patient's difference between indexes differed from that of the controls.

To verify the presence of bimanual coupling interference in the patient's performance compared with the controls, for the right and the left hand independently:

i) we compared the congruent and the incongruent index in the vision condition;

ii) we compared the congruent and the incongruent index in the no vision condition.

To further investigate the influence of the visual input on the performance, we compared the *bimanual coupling index (incongruent OI minus congruent OI)* registered in vision and no vision conditions between the patient and controls, independently for the right and the left hand, through the Revised Standardized Difference Test (Crawford & Garthwaite, 2005; Crawford, et al., 2010). Thus, the higher the index, the higher the bimanual coupling. The set of analyses described for the OI was successively run for S and V.

Results.

Ovalization index (OI).

Controls. According to the repeated measures ANOVA, when the right hand was analyzed, a significant main effect of *Index* (congruent M = 0.008; SD = 0.082; incongruent M = 8.36; SD = 1.21) emerged [$F(1, 14) = 47.05$; $p < 0.001$; partial $\eta^2 = 0.77$], in absence of a significant main effect of *Condition* (vision M = 4.3; SD = 0.61; no vision M = 4.063; SD = 0.69) $F(1, 14)= 0.46$; $p = 0.5$; partial $\eta^2 = 0.032$), as expected. Moreover, no significant interaction *Index*Condition* (vision congruent M = 0.02; SD = 0.45; vision incongruent M = 8.8; SD = 5.74; no vision congruent M = -0.03; S = 0.41; no vision incongruent M = 8.62; SD = 4.74) [$F(1, 14)= 0.79$; $p = 0.38$; partial η2 = 0.054] was found. A similar pattern emerged for the left hand, with a significant main effect of *Index* (congruent M = 0.05; SD = 0.12; incongruent M = 8.98; SD = 1.204) [$F(1,12) = 57.17$; $p < 0.0001$; partial $\eta^2 = 0.82$], in absence of a significant main effect of *Condition* (vision M = 4.84; SD = 0.83; no vision M = 4.18; SD = 0.54) [$F(1, 12) = 1.016$; $p = 0.33$; partial $\eta^2 = 0.078$) or a significant interaction *Index*Condition* (vision congruent M = 0.2; SD = 0.45; vision incongruent M = 8.33; DS = 4.52; no vision congruent M = -0.06; SD = 0.73; no vision incongruent M = 8.62; SD = 5.88) [$F(1, 12) = 1.97$; $p = 0.18$; partial $\eta^2 = 0.14$]. Thus, in line with the previous literature, we observed the bimanual coupling effect in controls for both right and left hand. Interestingly, we reported the effect also when the task was performance in absence of any visual input.

Vision condition: controls vs single-case. Considering the patient's performance, the mean score for the right hand relative to the congruent index was -0.06, and 2.47 for the incongruent index. About the left hand, the mean score was -0.19 for the congruent index, and 7.78 for the incongruent index (Figure 3, right panels).

[Figure 3 around here]

In Figure 4, examples of the patient's and one healthy control's trajectories in the incongruent bimanual trials were reported.

[Figure 4 around here]

About the right (affected) hand, the difference between the congruent and the incongruent index relative to the patient's performance was not different from controls [$t(15) = 0.76$; $p = 0.45$; effect size = 0.82 (95% CI = 0.21 to 1.47). The same result was found about the left hand [$t(15) = 0.45$; $p = 0.65$; effect size = -0.48 (95% CI = -1.03 to 0.05)]. This set of analyses suggested the absence of

any difference between the patient's and the controls' performance in the visual condition of the experimental task, for both right and left hand.

No vision condition: controls vs single-case. Considering the patient's scores, the mean score for the right hand relative to the congruent index was 1.62, and 0.05 for the incongruent index. About the left hand, the mean score was 1.71 for the congruent index, and 7.71 for the incongruent index (Figure 5, right panels).

[Figure 5 around here]

In Figure 4, examples of the patient's and one healthy control's trajectories were shown.

About the right hand, the difference between the congruent and the incongruent index relative to the patient's performance was significantly different from healthy participants' performance [t(15) = 3.88; p = 0.001; effect size = 4.179 (95% CI = 2.66 to 5.9)]. Specifically, the OI was larger in the incongruent condition than the congruent condition for controls as expected. However, this pattern was not observed in the patient's performance. Thus, when the visual feedback was precluded, the normal movement of the intact hand did not induce a coupling effect on the movement of the affected one.

However, such a difference did not emerged for the left hand [t(15) = 1.91; p = 0.07; effect size = 2.06 (95% CI = 1.14 to 3.11)]; this means that, even when the visual feedback was precluded, the movement of the affected hand induced a coupling effect on the movement of the unaffected one.

Comparison between vision and no vision conditions.

Since we found a different pattern between controls' and the patient's performance in relation to the presence (no difference) or the absence (a significant difference) of the visual input for the right hand, we ran a comparison between these conditions. Considering the previous results, the difference would be driven by the patient's OI (higher for the vision condition, lower for the no vision condition), while for healthy controls we might expect a high value in both conditions. Instead, we expected no difference about the left hand. Regarding the right hand, significant different results were found between vision and no vision conditions for patient and controls [t(15) = 1.793; one-tailed p value = 0.046; effect size = 1.982; 95% CI = 0.893 to 3.182], in line with our hypothesis. In contrast, no difference emerged about the left hand [t(15) = 0.315; one-tailed p = 0.37; effect size = 0.340 (95% CI = -0.168 to 0.860], again in line with our expectation. Thus, we were able to confirm that, in the case of a central proprioceptive loss, the absence of the visual input prevented the onset of the bimanual coupling effect for the affected right hand.

Vertical component of the drawing trajectory (S).

Controls. According to ANOVA, when the right hand was analyzed, a significant main effect of *Index* (congruent M = 0.43; SD = 1.81; incongruent M = -2.01; SD = 4.53) emerged [F(1, 11) = 6.23; p = 0.03; partial $\eta^2 = 0.36$), in absence of a significant main effect of *Condition* (vision M = -0.15; SD = 0.67; no vision M = -0.6; SD = 0.62) (F(1, 11)= 0.2; p = 0.66; partial $\eta^2 = 0.01$) or a significant interaction *Index*Condition* (vision congruent M = 0.433 SD = 1.81; vision incongruent M = -2.01; SD = 4.53; no vision congruent M = -0.11; SD = 1.7; no vision incongruent M = -1.78; DS = 5.7) [F(1, 11)= 3.97; p = 0.071 partial $\eta^2 = 0.26$]. The same pattern was found about the left hand: a significant main effect of *Index* (congruent M = -1.9; SD = 2.01; incongruent M = 0.15; SD = 3.02) emerged [F(1, 11) = 9.66; p = 0.01; partial $\eta^2 = 0.46$), in absence of any main effect of *Condition* (vision M = 0.7; SD = 0.52; no vision M = -1.09; SD = 0.83) (F(1, 11)= 0.19; p = 0.66; partial $\eta^2 = 0.017$) or any significant interaction *Index*Condition* (vision congruent M = 0.15; DS = 30.2; vision incongruent M = -1.9; SD = 2.01; no vision congruent M = -1.81; SD = 1.71; no vision incongruent M = -0.43; SD = 2.21) [F(1, 11)= 0.23; p = 0.63 partial $\eta^2 = 0.021$]. Thus, the vertical extension of the line relative to the incongruent condition was shorter respect to the congruent condition, independently from the visual input.

Vision condition: controls vs single-case. Considering the patient's performance, the mean score for the right hand relative to the congruent index was -0.88, and -7.1 relative to the incongruent index. About the left hand, the mean score was -2.07 for the congruent index, and -8.02 for the incongruent index.

With regard to the right hand, no significant difference in S value were found between congruent and incongruent conditions for patient and controls [t(11) = 0.45; p = 0.65; effect size = 0.51 (95% CI = -1.32 to 0.24). Instead, for the left hand, a significant difference between patient and controls emerged [t(11) = 2.58 p = 0.025; effect size = -2.96 (95% CI = -4.79 to -1.41)]. Considering the negative sign of the mean, the line vertical extension drawn with the left hand relative to the incongruent index was shorter than in the congruent index; moreover, the difference between the two indexes was larger than what observed in controls. Instead, such a difference was not reported for the right (affected) hand.

No vision condition: controls vs single-case. Considering the patient's performance, the mean S for the right hand relative to the congruent index was -1.98, and -0.81 for the incongruent index. As

to the left hand, the mean S was -1.81 for the congruent index and -2.26, for the incongruent index. For the right hand, the difference between the congruent and incongruent conditions was not different between the patient and the control sample [t(13) = 0.83; p = 0.42; effect size = -0.89 (95% CI = -1.56 to -0.26). The same results emerged for the left hand [t(13) = 0.69; p = 0.49; effect size = -0.76 (95% CI = 0.15 to 1.4].

Comparison between vision and no vision conditions.

In line with the previous analyses performed about the OI, we ran a comparison between conditions, since different pattern between controls and patient in relation to the presence of the visual input for the left hand, but not about the right hand, was found. *A priori*, we might expect a significant difference between patient and controls in S for the left hand, but not for the right hand.

About the right hand, controls reported a mean of -3.34 (SD = 2.04) for the vision condition, and a mean of -1.67 (SD = 5.96) for the no vision condition. The patient reported a mean of 6.22 for the vision condition, and a mean of 1.17 for the no vision condition. No significant difference emerged between these means [t(10) = 1.268; one tailed p = 0.11; effect size = 1.407 (95% CI = -2.333 to -0.572], as expected. About the left hand, controls reported a mean of 1.84 (SD = 2.77) for the vision condition and a mean of 2.25 (SD = 2.15) for the no vision condition. The patient reported a mean of -5.95 for the vision condition, and a mean of -0.45 for the no vision condition. No significant result emerged [t(10) = 1.426 one tailed p = 0.09; effect size = -1.623 (95% CI = -3.148 to -0.302), in contrast with our prediction.

We might conclude that the vertical extension of the line was not affected by the presence of the visual input.

Average drawing velocity (V).

Controls. As regards the right hand, a main effect of *Condition* emerged [F(1,11) = 16.67; p = 0.002; partial $\eta^2 = 0.602$], since controls reported lower V in the no vision condition (M = -46.47; SD = 9.69) than in the vision condition (M = -7.57; SD = 4.43); in other words, controls drew faster when they performed the task in vision condition, in contrast to when they were blindfolded. No main effect of *Index* (incongruent M = -28.5; SD = 10.12; congruent M = -25.55; SD = 7.76) [F(1,11) = 0.046; p = 0.83; partial $\eta^2 = 0.004$] or a significant interaction *Index*Condition* (vision congruent M = -2.18; SD = 24.84; vision incongruent M = -48.9; SD = 45.73; no vision congruent M = -8.12; SD = 41.6, no vision incongruent M = -36.2; SD = 54.02) emerged [F(1,11) = 1.54; p = 0.24; partial $\eta^2 = 0.12$]. When the left hand was analyzed, no main effect of *Condition* (vision M =

-14.83; SD = 9.05; no vision M = -18,02; SD = 3.14) F(1,11) = 0.16; p = 0.69; partial η^2 = 0.015] or *Index* (congruent M = 13.81; SD = 5.28; incongruent M = -19.04; SD = 7.98) [F(1,11) = 0.45; p = 0.51; partial η^2 = 0.04] emerged; moreover, no significant interaction *Index*Condition* was observed (vision congruent M = -20.3; DS = 14.23; vision incongruent M = -17.8; SD = 46.76; no vision congruent M = -16.2; SD = 14.42; no vision incongruent M = -10.8; SD = 23.44) [F(1,11) = 0.021; p = 0.88; partial η^2 = 0.002]. Only for the right hand, the drawing velocity was reduced in the incongruent index contrary to the congruent index. For the left hand, such a difference did not emerge. Moreover, this pattern was not related to the presence of visual input.

Vision condition: controls vs single-case. Considering the patient's performance, the mean V for the right (affected) hand relative to the congruent index was 43.42, and 46.35 relative to the incongruent index. About the left hand, the mean V was -23.36 for the congruent index, and -80.82 for the incongruent index. For the right hand [t(10) = 1.58; p = 0.74; effect size = -0.37 (95% CI = -1.43 to 0.63) and left hand [t(10) = 1; p = 0.34; effect size = 1.13 (95% CI = 0.3 to 2.05)], no difference between patient and controls was found.

No vision condition: controls vs single-case. About the right hand, the patient reported a V mean of 1.19 for the congruent index, and of -0.523 for the incongruent index. About the left hand, the patient reported a V mean was of -13.57 for the congruent index, for the incongruent index of -28.6. For the right hand [t(13) = 0.29 p = 0.77; effect size -0.32 (95% CI = -0.89 to 0.23) and the left hand [t(13) = 1.13; p = 0.27, effect size = 1.25 (95% CI = 0.56 to 2.01)] no difference between patient and controls was found.

Because of this pattern of results, no further analysis was run.

Discussion

The aim of the present study was to investigate the effect of a central loss of proprioceptive processing on spatial bimanual coupling. The single-case patient presented in this paper suffered of a conscious loss of proprioceptive information relative to the right hand when out of the visual control, as consequence of a left brain damage involving the postcentral gyrus and the superior parietal gyrus. We compared our patient's performance with a sample of healthy individuals in a new version of the traditional Circles-Lines Coupling Task (Garbarini et al., 2012, 2013, 2014, 2015ab, Piedimonte et al., 2018; Della Gatta et al., 2017; Burin et al., 2019) by studying lines' trajectories for both hands. The worth of the present study was to report experimental evidence of

the influence of the spared hand movements on the trajectories of the impaired hand in a bimanual coupling task, given that our patient was able to move the affected hand. Indeed, in our group's previous studies (Garbarini et al., 2012, 2013, 2014), we were not able to itemise this effect, since we studied patients affected by paresis of the controlesional limb.

Focusing on healthy controls, in this study we successfully replicated the bimanual coupling effect. The line ovalization - that is commonly recognized as an index of this phenomenon (Franz, 1997; Garbarini and Pia, 2013) – was significantly higher in the incongruent condition (i.e. one hand drawing lines, the other hand drawing circles) than in the congruent bimanual condition (i.e. both hands drawing lines), and in the unimanual condition (i.e. one hand drawing lines, the other hand was in the rest position). Interestingly, this effect emerged not only when the task was performed in full vision of hands' movements (Figure 3, left panels), but also when healthy participants were blindfolded during the task execution (Figure 5, left panels). To our knowledge, this was the first evidence of the presence of bimanual coupling effect, in absence of visual input. Moreover, in this work we described the performance in terms of vertical component of the drawing trajectory and of the average drawing velocity. We found that the vertical extension of the line tended to be shorter in the incongruent condition respect to the congruent one. This effect was observed for both hands. This result mirrored what reported by Ivry and colleagues (2004) who stated that *"the incongruent condition was quite taxing"* (p. 264), possibly explaining why participants drew shorter lines. About the drawing velocity, we found that healthy participants were slower in the incongruent condition compared with the congruent one, when lines were drawing with the right hand. On the contrary, this difference did not emerge for the left hand. This result, even though preliminary, might be suggestive of handedness-related asymmetry in Circles-Lines Coupling Task, as reported in previous literature about bimanual coordination (Gerloff & Andres, 2002; Viviani et al., 1998, de Poel et al., 2006; Serrien et al., 2012). In previous studies in which Circles-Lines Coupling Task was adopted (Garbarini et al., 2012, 2013, 2014, 2015ab), the two components of lines' vertical extension and drawing velocity were not computed, limiting further interpretations of our results. However, they might encourage future investigation in which not only spatial, but also temporal drawing components will be considered.

Focusing on the single-case, when the task was performed in the vision condition, the patient's behaviour mirrored the controls' performance; in other words, we observed the bimanual coupling effect (Figure 3, right panels) on both hands. Indeed, the affected hand was influenced by the concomitant movement of the spared hand, and *vice versa*. However, when the patient was blindfolded (i.e. no vision condition), the trajectory of the impaired right hand was not influenced

by the concomitant movement of the spared left hand; thus, the interference effect did not arise (Figure 5, right panels). On the contrary, the left hand was influenced by the movement of the right affected hand, showing a higher ovalization index in the incongruent bimanual condition compared with the congruent one, as in healthy controls. Overall, the bimanual coupling effect only pertained to the left spared hand, while the right affected hand was not influenced by the simultaneous movement of the other hand, when visual input was not available. Therefore, we might argue that when proprioception is lost, the visual input might play a crucial role in the interference effect of the unaffected hand on the affected one. Also, according to our results, this effect might be not related to the drawing velocity or to the vertical extension of the line trajectories.

How should the performance of our patient be discussed? According to the Intermanual Cross-talk Model (Marteniuk and MacKenzie, 1980), the bimanual coupling effect arises from the coordination and assimilation of two concurrent, but dissimilar/incongruent motor plans. Accordingly, the absence of the coupling effect in our patient's performance might be read as a failure in the motor coordination of the affected right hand with the movement of the unimpaired left hand. Nevertheless, in our patient there was no lesion in the two neural pathways (the corpus callosum and the corticospinal tract) underpinning the Intermanual Cross-Talk (Marteniuk and MacKenzie, 1980). Moreover, this model would not explain why, during the vision condition (but not in the no vision condition), the right hand properly assimilated the left hand motor plan.

In our patient, the absence of central processing of proprioceptive information seemed to preclude the emerging of the bimanual coupling about the impaired right hand, despite intact motor behaviour and motor intentionality. The awareness about the hand position may play as a trigger, prompting the reciprocal coordination between hands' motor plans. This would mean that in the absence of visual information, a proper proprioceptive feedback would be necessary for the integration of the current motor plan of one hand with the other hand. If the proprioceptive feedback is impaired, the motor output might then be executed, but ignoring the concurrent contralateral motor plan. Consequently, the bimanual coupling effect would not arise. The underling mechanism of such an effect should be probed further. However, it is well known that the initial motor plan is weighted according to the on-line sensory feedback (Cruse et al., 1987). The motor system generates the appropriate motor output accordingly to the aim of action, while the motor plan is used as an *efference copy* to predict the sensory feedback (*Forward Model)* (Kawato, 1999). If the actual sensory feedback differs from the predicted one, the original motor plan is updated. Consequently, if the sensory information originated from the affected hand is not correctly processed due to the alteration of the central proprioception (as in in the case of our patient), the

system cannot detect any discrepancy between the predicted sensory feedback and the current feedback; thus, the motor plan would not be updated. According to our hypothesis, the bimanual coordination actually occurs at the level of motor planning and intentionality (Franz and Ramachandran, 1998; Garbarini and Pia, 2013); however, when the proprioceptive feedback is defective, the motor plan assimilation might be hampered. In our patient, the bimanual interference was not observed when the task was performed out of vision, but it emerged when the patient looked at the hands' movements. We might speculate that the availability of the visual input might compensate (at least partially) for the central proprioceptive loss, triggering the motor plan's update. This seems to be in line with our patient's report about difficulty in correctly localizing the impaired right hand, but only when it was out of the visual control. Thus, the role of vision and, overall, the integration of multiple sensory input in bimanual coordination should be further investigated.

This single-case study pertained to spatial bimanual coordination. Specifically, the interference of the unaffected hand on the motor behaviour of the affected one and vice versa, in the case of a pure central loss of proprioception, was studied. In previous studies, motor intentionality relative to paralyzed (Garbarini et al., 2012; 2013) or absent limb (Franz and Ramachandran, 1998) on the spared one was investigated; in other words, only the performance of the unaffected limb was directly tested. Instead, our patient was still able to move both limbs to perform the task, allowing us the investigation of both (the affected and the unaffected) arms. Future studies will help to explore our hypothesis. Particularly, it would be useful to perform our experimental paradigm in healthy participants to verify the effect of altered central proprioceptive feedback on bimanual coupling. Repetitive Transcranial Magnetic Stimulation might be a useful tool: for example, van der Berg and colleagues (2010) used this technique to temporarily disrupt left versus right premotor cerebral cortex feedback during a temporal bimanual task. In addition, the experimental manipulation of peripheral proprioceptive input through anesthesia and ischemic nerve block technique, as well as the vibrotactile stimulation of limbs might be used. It would be noticed that in this manuscript we described the drawing performance in terms of the ovalization index of the lines, in line with previous studies (Garbarini et al., 2012, 2013, 2014, 2015ab; Piedimonte et al., 2018; Della Gatta et al., 2017; Burin et al., 2019). Nevertheless, the effect of bimanual coupling on circle drawing can be investigated by introducing two other experimental conditions (i.e. one hand drawing a circle; both hands drawing a circle) in the procedure. However, it might be considered that while both (line ovalization and circle ovalization) effects can be observed, humans might be not completely able to draw a perfect circle. In other words, any circle is already ovalized; such distortion is numerically larger than the one that can be observed in line drawing; consequently a

lower OI sensitivity might be expected when circle (and not line) is studied. Moreover, as done in previous studies (Garbarini et al., 2012, 2013, 2014, 2015ab; Piedimonte et al., 2014, 2018; Della Gatta et al., 2017; Burin et al., 2019), we investigated the spatial characteristics of the line drawing by one hand, through the OI; moreover, only one hand at the time (and not their coordination, as done generally in temporal bimanual tasks) was assessed. In the future, temporal characteristics of hands' movements would be assessed. Furthermore, possible handedness-related asymmetry in Circles-Lines Coupling Task, as done elsewhere (Gerloff & Andres, 2002; Serrien, et al. 2003, Viviani, et al., 1998, de Poel et al., 2006; Serrien et al., 2012), would be considered.

From an anatomical point of view, our patient suffered of a cerebral lesion involving not only the postcentral gyrus, that corresponds to the primary somatosensory cortex, but also the superior parietal gyrus, that is part of the dorsal visual pathways (Ungerleider and Mishkin, 1982; Goodale and Milner, 1992; Culham and Valyear, 2006). This pathway is crucially involved in spatial perception and action (Goodale and Milner, 1992; Culham and Valyear, 2006), motor planning and visuomotor control (Karnath & Perenin, 2005; Perenin & Vighetto, 1988), and praxis (Buxbaum et al., 2007; 2018). Nevertheless, in our single-case, the possible presence of ideational and ideomotor apraxia was excluded through a qualitative neuropsychological assessment. It should be noticed that during the neurological examination, our patient showed dysmetric movements with both limbs during the "finger to nose test" when it was performed with eyes closed. This finding might be consistent with the hypothesis of the critical role of aberrant proprioceptive information in signaling body shape, body position and movements (Proske and Gandevia, 2002) and in performing action (Blangero et al., 2007; Dijkerman and de Haan, 2007). Nevertheless, no difficulty in visuomotor guidance was subjectively reported by the patients or observed (even though not specifically tested) by clinicians.

Besides any possible interpretations of our findings, and the limited generalizability of our results, the current case-report study demonstrated that central proprioceptive information contributes importantly to the bimanual spatial coupling effect. The motor intentionality, namely the subjective experience of the intention to act, determining the sense of agency (Haggard, 2005) is crucial for providing bimanual coordination; nevertheless, the role of primary sensory information might not be of less importance in promoting limbs' interactions.

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Table 1. Neuropsychological assessment and results. For each cognitive domain, the neuropsychological test was reported. Raw scores, adjusted scores, and the cut-off computed according to the Italian normative data were reported. * indicates when the score was below the normative cut-off.

Neuropsychological test	Italian normative reference	Maximum score	Raw score	Adjuested score	cut-off	
Global cognitive functioning						
Mini Mental State Examination	Grigoletto et al., 1999	30	28	28	25	
Clock Drawing Test	Mondini et al., 2003	10	10	--	5	
Oral Denomination						
Nouns	Miceli et al., 2003	10	10	10	8.2	
Verbs		10	10	10	6.1	
Short Memory						
Digit Span Forward Test	Monaco et al., 2013	9	5	5	3.75	
Corsi's Span Forward Test		9	3	3	3.5	*
Verbal Long Memory						
Short Story Test	Novelli et al., 1986	28	12.5	12	8	
Executive Functions						
Frontal Assessment Battery	Appollonio et al., 2005	18	16	16.30	11.60	
Digit Span Backward Test	Monaco et al., 2013	9	3	3.02	2.65	
Phonemic Fluency	Costa et al., 2014	--	28	30.73	17.77	
Semantic Fluency		--	41	39.96	28.34	
Stroop's Test – time	Caffarra et al.,	--	39	38.5	36.91	*

Stroop's Test – error	2002	30	0	0	4.23
Constructional Praxis					
Copy of drawings	Caltagirone et al., 1995	12	10	10.1	7.18
Selective attention					
Attentional Matrices I	Spinnler and Tognoni, 1987	10	4	--	6 *
Attentional Matrices II		50	34	33	24

Figure 1. MRI performed at the time of the experiment showing the outcome of the meningioma removal surgery characterized by leukomalacia (maximum diameters 31.9 mm x 8,01 mm) and gliosis (maximum diameters 36.77 mm x 15.07 mm) in postcentral gyrus and in superior parietal gyrus.

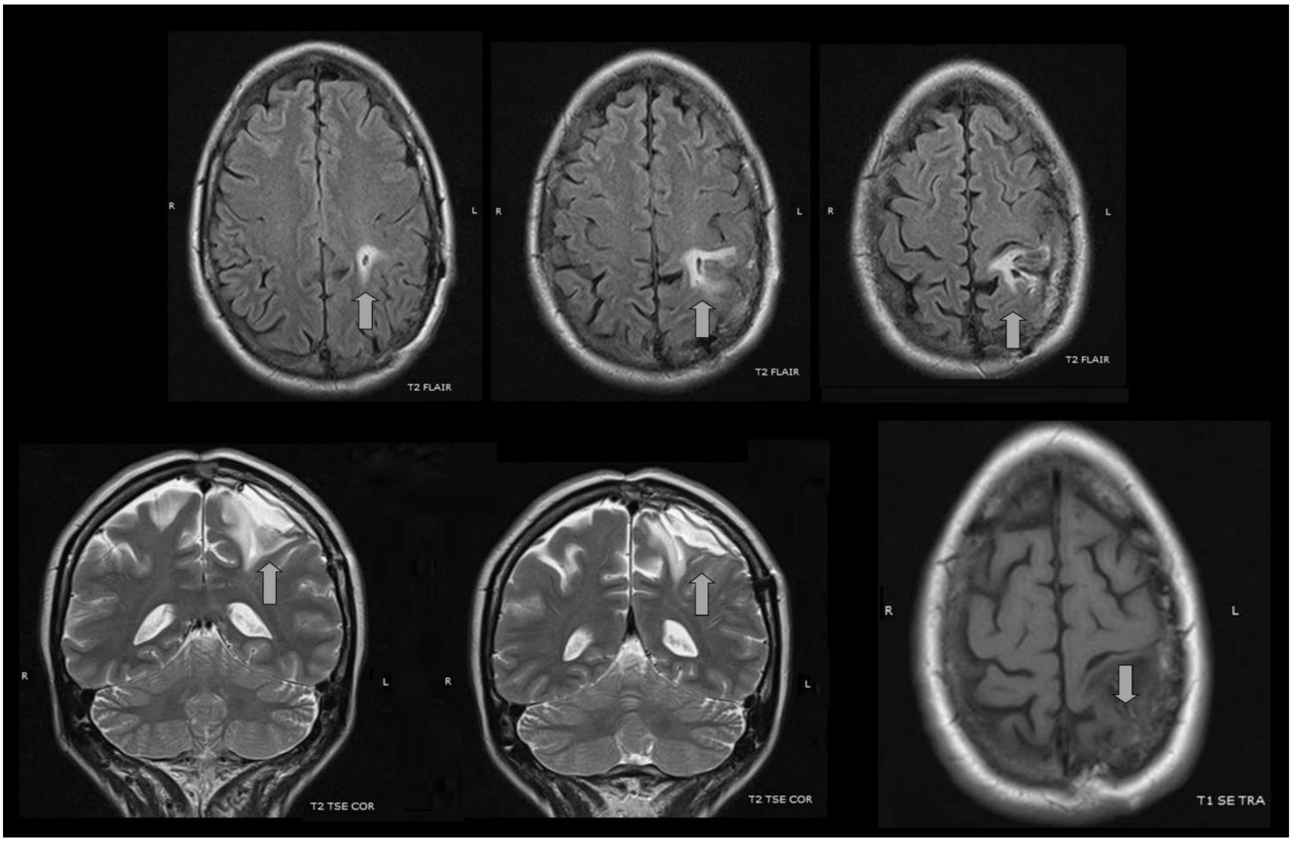


Figure 2. Representation of the experimental conditions of the Circles-Lines Coupling Task (on the left) and of the experimental set-up (on the right). The task was performed in vision and in no vision condition.

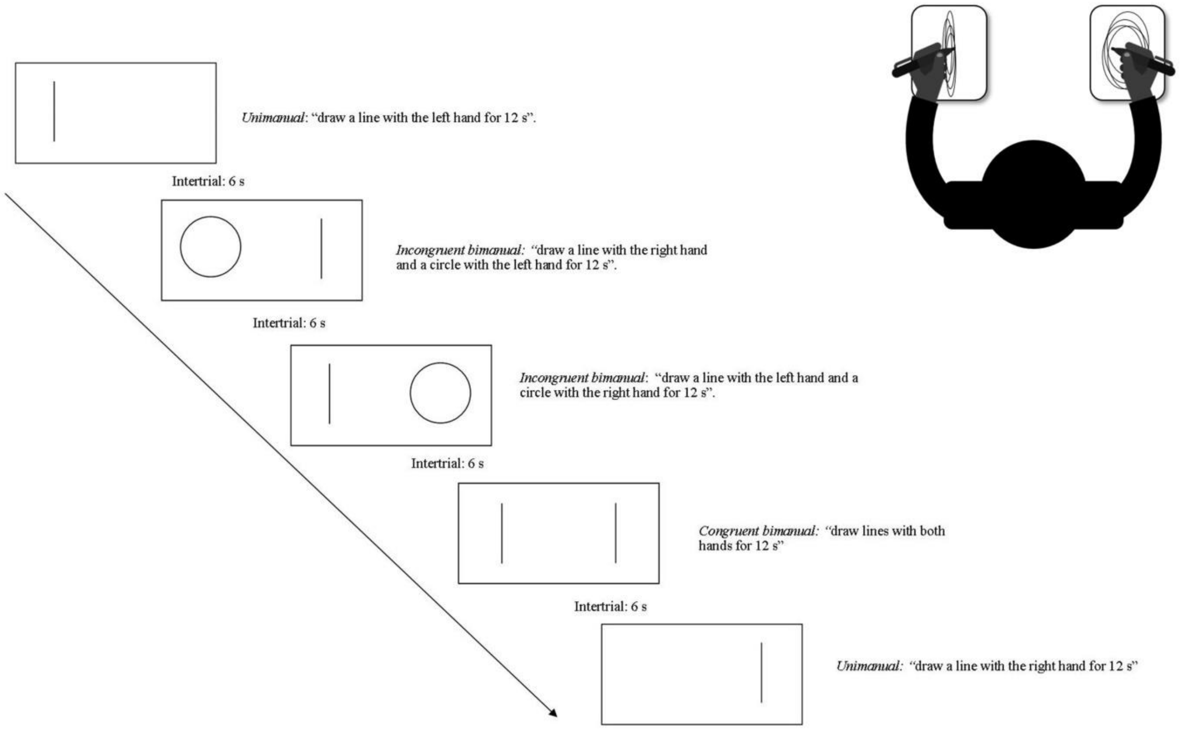


Figure 3. Bimanual Coupling Task - vision condition. Left panel: about the healthy controls' performance, the Ovalization index (OI) mean (vertical bars) and the standard error (horizontal lines) for the congruent index and the incongruent index, relative to the right hand (upper part) and the left hand (below part) were reported. Specifically, the *congruent index* was computed as the difference between the mean of the OI registered in the *congruent bimanual* trials and the mean of OI relative to the *unimanual* trials; for the *incongruent index*, the mean of the OI registered in the *incongruent bimanual* trials was subtracted from the mean of OI relative to the *unimanual* trials. **Right panel:** about the patient's performance, the mean OI (horizontal bars) for the congruent index and the incongruent index, relative to the right hand (upper part) and the left hand (below part), was reported. The p-value was shown; a value higher than 0.05 (not significant) indicated that the difference between the two indexes about the patient's performance did not differ compared with the difference registered for the controls. Patient and controls reported a similar performance: the OI reported in the congruent index was lower compared with incongruent index, in line with the expected effect.

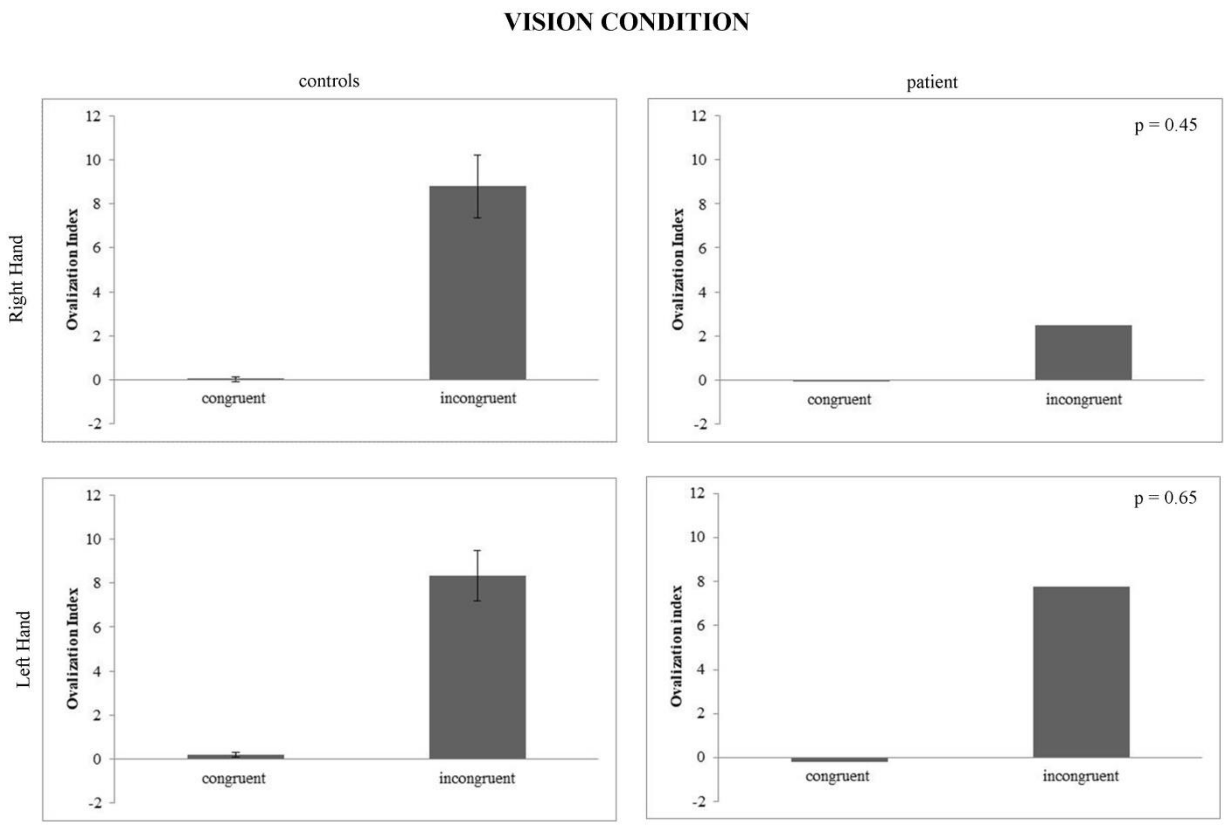


Figure 4. Examples of the patient's (right panel) and a healthy participant's (left panel) for the line trajectories of the right hand and the left hand in the *incongruent bimanual condition* (i.e. when participant drew lines with one hand, and circles with the other) were showed relative to the vision condition (upper part) and no vision condition (below part). Lat.-coord. = the horizontal displacement in mm; up-down coord = vertical displacement in mm. For each picture, we reported the OI). Thus, it might be noticed that in the no vision condition, the patient's trajectory relative to the right hand was clearly less ovalized (i.e. less displaced on the horizontal axys) in comparison with the healthy control: this suggested the absence of bimanual coupling. Such a difference was not reported in the other conditions, in which bimanual coupling emerged.

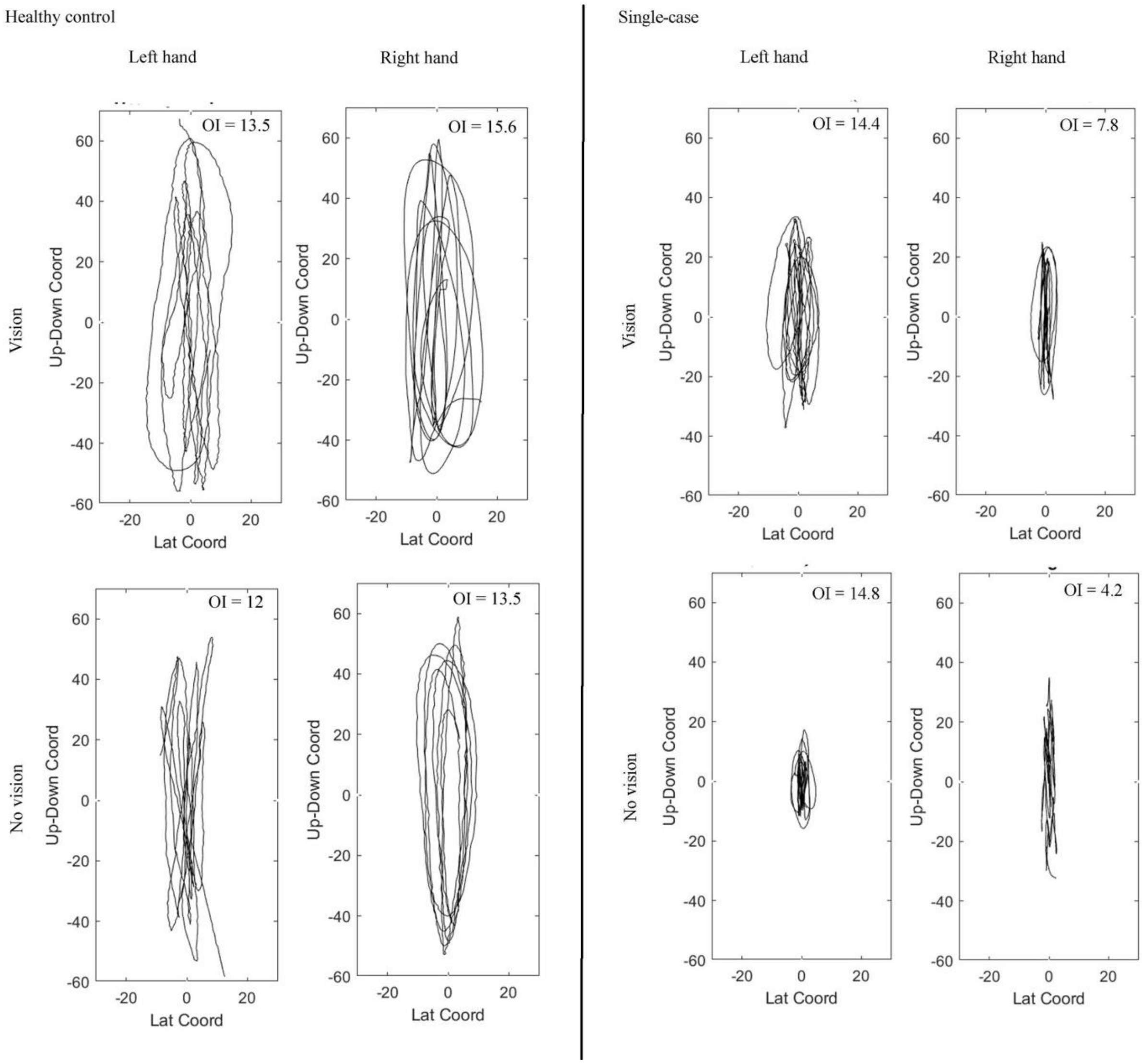


Figure 5. Bimanual Coupling Task – no vision condition. Left panels: about the healthy controls' performance, the Ovalization index (OI) mean (vertical bars) and the standard error (horizontal lines) for the congruent index and the incongruent index, split for the right hand (upper part) and the left hand (below part) were reported. Specifically, the *congruent index* was computed as the difference between the mean of the OI in mm registered in the *congruent bimanual* trials and the mean of OI relative to the *unimanual* trials; for the *incongruent index*, the mean of the OI registered in the *incongruent bimanual* trials was subtracted from the mean of OI relative to the *unimanual* trials. **Right panels:** about patient's performance, the mean OI (vertical bars) for the congruent index and the incongruent index, split for the right hand (upper part) and the left hand (below part) was reported. The p-value was shown; a value higher than 0.05 (not significant) suggested that the difference between the two indexes registered about the patient's performance did not differ respect compared with the controls' performance; in other words, patient and controls reported a similar behaviour. Instead, if the value was lower than 0.05 (significant, in bold), it indicated that such a difference was not comparable between patient and controls: this was the case of the patient's performance for the right hand. The difference between the patient's OI relative to the congruent condition and the incongruent condition indexes registered about the right hand was significantly different when compared with the controls, who reported the expected pattern (i.e. the congruent index was significantly lower than the incongruent index).

NO VISION CONDITION

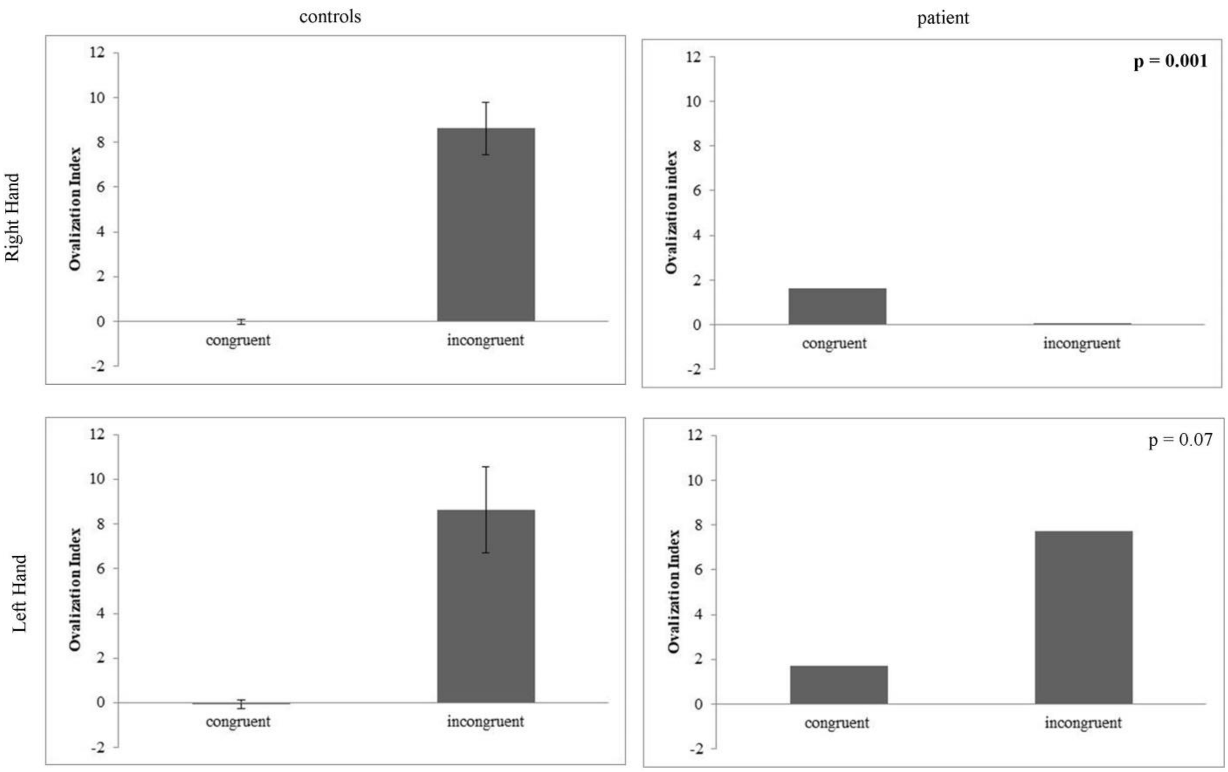
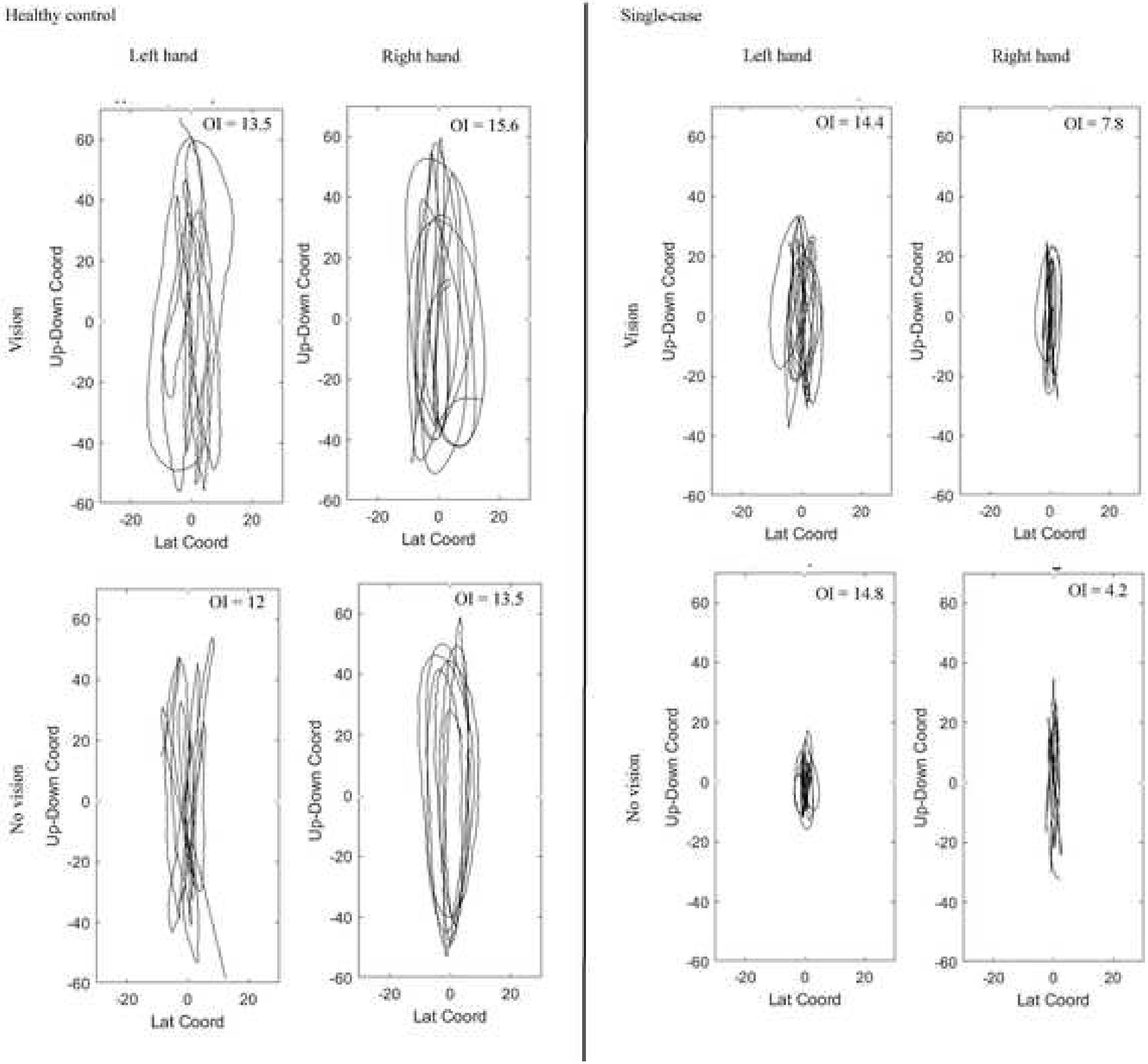


Figure 4


Healthy control
Left hand
Right hand
Single-case
Left hand
Right hand
Vision
No vision
OI = 13.5
OI = 15.6
OI = 14.4
OI = 7.8
OI = 12
OI = 13.5
OI = 14.8
OI = 4.2
Up-Down Coord
Lat Coord