Sensorimotor Integration during Rubber Hand Illusion in Normal Subjects and Subjects with Parkinson’s Disease

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Abstract

Rubber hand illusion (RHI) measures visuo-tactile multisensory integration. Non-motor symptoms are well recognized in Parkinson’s disease (PD) and PD patients have impaired sensation and sensorimotor integration. We hypothesized that 1) RHI decreases sensorimotor integration in healthy subjects 2) PD patients show reduced RHI and less modulation of sensorimotor integration by RHI. We used transcranial magnetic stimulation to examine short- and long-latency afferent inhibition (SAI and LAI), which measures the influence of sensory input on the primary motor cortex (M1), and the posterior parietal cortex (PPC)-M1 interactions during RHI. In healthy subjects, we found reduced SAI and LAI during RHI, and stronger RHI correlated with greater inhibitory PPC-M1 interactions. PD patients showed normal RHI, but had no correlation between RHI strength and PPC-M1 interactions. Our results show that RHI modulates both early and late stages of sensorimotor integration in healthy subjects and this effect of RHI is altered in PD.
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Table of Contents

Acknowledgments ........................................................................................................ iii
Contributions ................................................................................................................ v
Table of Contents .......................................................................................................... vi
List of Abbreviations .................................................................................................... xii
List of Figures ................................................................................................................. xv
List of Tables .................................................................................................................. xvi

1 LITERATURE REVIEW ..............................................................................................1
  1.1 Parkinson’s Disease (PD) .................................................................................... 1
    1.1.1 Parkinson’s disease and its motor symptoms .............................................. 1
    1.1.2 Sensory Symptoms and Sensory Impairments in Parkinson’s disease ....... 2
    1.1.3 Deficits in Sensorimotor Integration in Parkinson’s Disease .................... 4
  1.2 Physiology and Pathophysiology of Sensorimotor Integration ......................... 7
    1.2.1 Neurophysiology of Sensorimotor Integration in Healthy Populations ...... 7
    1.2.2 The Use of Transcranial Magnetic Stimulation (TMS) to Assess Sensorimotor Integration ................................................................. 8
      1.2.2.1 Transcranial Magnetic Stimulation (TMS) ........................................... 8
      1.2.2.2 Short-latency Afferent Inhibition (SAI) and Long-latency Afferent Inhibition (LAI) in Healthy Populations ................................. 9
      1.2.2.3 Short-latency Afferent Inhibition (SAI) and Long-latency Afferent Inhibition (LAI) in PD Patients ........................................... 12
  1.3 Multisensory Integration ....................................................................................... 14
    1.3.1 Multisensory Sensory Integration and Sensorimotor Integration in Healthy Populations ................................................................. 14
    1.3.2 Neural Correlates of Multisensory Integration ........................................... 16
    1.3.3 The Role of Posterior Parietal Cortex in Multisensory Integration and Sensorimotor Integration ......................................................... 17
    1.3.4 Functional Interactions between the Left Posterior Parietal Cortex (PPC) and Ipsilateral Primary Motor Cortex (M1) Examined by Transcranial Magnetic Stimulation (TMS) ........................................ 21
    1.3.5 Rubber Hand Illusion as a Tool to Investigate Multisensory Integration ... 24
1.3.5.1 Behavioral Studies of Rubber Hand Illusion ........................................24
1.3.5.2 The Role of Cognitive Process during RHI ........................................27
1.3.5.3 RHI influences on Motor Responses ..................................................28
1.3.5.4 Application of RHI in Neuropsychiatric Disorders ..............................28
1.3.5.5 Brain Regions Involving in Multisensory Integration for Own Body and Rubber Hand Illusion ..........................................................29
1.3.5.6 Posterior Parietal Cortex and Rubber Hand Illusion ............................30
1.3.6 Multisensory Integration in PD patients ..................................................31
1.3.6.1 Multisensory Integration and its Involvement in Sensorimotor Integration in PD patients at the Behavioral Level .............................32
1.3.6.2 Posterior Parietal Dysfunction in PD patients .....................................33

2 RESEARCH AIMS and HYPOTHESIS ........................................................................35
2.1 Objectives of the Present Thesis ......................................................................35

2.1.1 Study One: Modulation of Sensorimotor Integration by Rubber Hand Illusion in Healthy Subjects .................................................................35

2.1.2 Study Two: Modulation of Sensorimotor Integration by Rubber Hand Illusion in Parkinson’s Disease Patients ................................................35

2.2 Hypotheses of the Present Thesis .....................................................................36

2.2.1 Study One: Modulation of Sensorimotor Integration by the Rubber Hand Illusion in Healthy Subjects .................................................................36

2.2.2 Study Two: Modulation of Sensorimotor Integration by the Rubber Hand Illusion in Parkinson’s Disease Patients ................................................36

3 STUDY ONE: Modulation of Sensorimotor Integration by Rubber Hand Illusion in Healthy Subjects ........................................................................37
3.1 Abstract ........................................................................................................37

3.2 Introduction ..................................................................................................38

3.3 Methods .......................................................................................................39

3.3.1 Subjects ....................................................................................................40

3.3.2 Rubber Hand Illusion (RHI) and behavioural assessments .......................40

3.3.3 Digital nerve stimulation (DNS) ................................................................41

3.3.4 Surface electromyography (EMG) recording ............................................41

VII
3.3.5 Transcranial magnetic stimulation (TMS) .................................................42
  3.3.5.1 Experiment 1: Influence of the RHI on SAI and LAI .........................42
  3.3.5.2 Experiment 2: The influence of the RHI on the interaction between the posterior parietal cortex (PPC) and the primary motor cortex (M1) .................................................................42
3.3.6 Experimental Designs ............................................................................44
3.4 Data Analysis .............................................................................................48
3.5 Results .......................................................................................................49
  3.5.1 Questionnaire on the Rubber Hand Illusion Experiences ...................49
  3.5.2 Proprioceptive judgment (PJ) ...............................................................50
  3.5.3 Experiment 1: Modulation of Short- and Long-latency Afferent Inhibition by RHI .............................................................53
  3.5.4 Experiment 2: Modulation of the PPC-M1 interaction by the RHI .......56
3.6 Discussion ................................................................................................59
  3.6.1 Behavioural results confirmed the synchronous condition induces RHI ...59
  3.6.2 The RHI Reduces Short-latency Sensorimotor Integration ...................59
  3.6.3 The RHI Reduces Long-latency Sensorimotor Integration Reduction of LAI with .................................................................60
  3.6.4 Inhibitory PPC-M1 interaction is associated with the strength of RHI ......62
  3.6.5 Clinical Implications of the findings ......................................................63
3.7 Conclusions ...............................................................................................64
3.8 Acknowledgements ....................................................................................64
4 STUDY TWO: Modulation of Sensorimotor Integration by Rubber Hand Illusion in Parkinson’s Disease .................................................................65
  4.1 Abstract ..................................................................................................65
  4.2 Introduction ..............................................................................................66
  4.3 Methods ..................................................................................................67
    4.3.1 Subjects ............................................................................................67
    4.3.2 Rubber Hand Illusion (RHI) and behavioral assessments .................68
    4.3.3 Digital nerve stimulation (DNS) .........................................................69
    4.3.4 Surface electromyography (EMG) recording .....................................69
4.3.5 Transcranial magnetic stimulation (TMS) .................................................................70
  4.3.5.1 Experiment 1: Measurement of short-latency afferent inhibition (SAI) and long-latency afferent inhibition (LAI)........................70
  4.3.5.2 Experiment 2: Measurement of the interaction between the posterior parietal cortex (PPC) and the primary motor cortex (M1) ...............................................................................70

4.3.6 Experimental Designs .............................................................................................71

4.4 Data Analysis ..............................................................................................................72
  4.4.1 Clinical Assessments ...............................................................................................72
  4.4.2 RHI Behavioural Assessments .................................................................................72
    4.4.2.1 Evaluation of the Questionnaire .........................................................................72
    4.4.2.2 Evaluation of the Proprioceptive judgment (PJ) task ........................................73

4.4.3 Assessment of Transcranial magnetic stimulation (TMS) Measurements ........................73
  4.4.3.1 Experiment 1: The modulation of Short-latency afferent inhibition (SAI) and Long-latency afferent inhibition (LAI) by RHI ........................................................................73
  4.4.3.2 Experiment 2: The modulation of Posterior parietal cortex (PPC)-Primary motor cortex (M1) interaction by RHI ................74

4.5 Results ........................................................................................................................75
  4.5.1 Clinical and demographic data ................................................................................75
  4.5.2 Behavioural assessments of Rubber Hand Illusion ................................................77
    4.5.2.1 Questionnaire on the rubber hand illusion experiences ....................................77
    4.5.2.2 Proprioceptive judgment (PJ) ............................................................................77

4.5.3 Modulation of short-latency afferent Inhibition (SAI) by Rubber Hand Illusion .................................................................................................................................80
  4.5.3.1 Comparison between Parkinson’s Disease Patients and Healthy Controls ..................80
  4.5.3.2 Dopaminergic Influence on the SAI modulation in Parkinson’s Disease Patients ................80

4.5.4 Modulation of Long-latency afferent Inhibition (LAI) by Rubber Hand Illusion .................................................................82
5.7.2 Disrupted and Compensatory Sensorimotor Integration Pathways in PD patients ................................................................. 108
5.7.3 The Influence of Dopaminergic Medications ........................................... 109
5.7.4 Possible Intervention Therapy for PD patients ...................................... 110
5.8 Conclusions .......................................................................................... 110
References ................................................................................................ 112
List of Abbreviations

aIPS       Anterior part of Intraparietal Sulcus
ANOVA      Analysis of Variance
cIPS       Caudal part of Intra Parietal Sulcus
CS         Conditioning Stimulus
DBS        Deep Brain Stimulation
DNS        Digital Nerve stimulation
DNS\textsubscript{23-TS} Digital Nerve Stimulation followed by Test Stimulus at Inter-stimulus Interval of 23ms
DNS\textsubscript{203-TS} Digital Nerve Stimulation followed by Test Stimulus at Inter-stimulus Interval of 203ms
EEG        Electroencephalogram
EMG        Electromyographic
FDG        Fluorodeoxy glucose
FDI        First Dorsal Interosseous
Fig        Figure
f-MRI      Functional Magnetic Resonance Imaging
HCs        Healthy Controls
IPS        Intraparietal Sulcus
ISIs       Inter-stimulus Intervals
LAI        Long-Latency Afferent Inhibition
LOC        Lateral Occipital Cortex
MEP        Motor Evoked Potentials
M1         Primary Motor Cortex
PA         Posterior-Anterior
PD         Parkinson’s Disease
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>PD-OFF</td>
<td>Patients with Parkinson’s Disease without Dopaminergic Medication State</td>
</tr>
<tr>
<td>PD-ON</td>
<td>Patients with Parkinson’s Disease with Dopaminergic Medication State</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
</tr>
<tr>
<td>PJ</td>
<td>Proprioceptive Judgment</td>
</tr>
<tr>
<td>PMv</td>
<td>Ventral Premotor Cortex</td>
</tr>
<tr>
<td>PPC</td>
<td>Posterior Parietal Cortex</td>
</tr>
<tr>
<td>Pre-SMA</td>
<td>Pre-Supplementary Motor Area</td>
</tr>
<tr>
<td>PT</td>
<td>Physiotherapy</td>
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<tr>
<td>RHI</td>
<td>Rubber Hand Illusion</td>
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<tr>
<td>RLS</td>
<td>Restless Leg Syndrome</td>
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<tr>
<td>rTMS</td>
<td>repetitive Transcranial Magnetic Stimulation</td>
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<tr>
<td>SAI</td>
<td>Short-Latency Afferent Inhibition</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SEPs</td>
<td>Somatosensory Evoked Potentials</td>
</tr>
<tr>
<td>SEM</td>
<td>Standard Error of the Mean</td>
</tr>
<tr>
<td>SLF</td>
<td>Superior Longitudinal Fasciculus</td>
</tr>
<tr>
<td>SMA</td>
<td>Supplementary Motor Area</td>
</tr>
<tr>
<td>SPL</td>
<td>Superior Parietal lobe</td>
</tr>
<tr>
<td>ST</td>
<td>Sensory Threshold</td>
</tr>
<tr>
<td>STDT</td>
<td>Somatosensory Temporal Discrimination Threshold</td>
</tr>
<tr>
<td>STN-DBS</td>
<td>Subthalamic Nucleus Deep Brain Stimulation</td>
</tr>
<tr>
<td>STS</td>
<td>Superior Temporal Sulcus</td>
</tr>
<tr>
<td>S1</td>
<td>Primary Sensory Cortex</td>
</tr>
<tr>
<td>S2</td>
<td>Secondary Sensory Cortex</td>
</tr>
<tr>
<td>TMS</td>
<td>Transcranial Magnetic Stimulation</td>
</tr>
<tr>
<td>TPJ</td>
<td>Temporoparietal Junction</td>
</tr>
<tr>
<td>TS</td>
<td>Test Stimulus</td>
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<tr>
<td>------</td>
<td>---------------</td>
</tr>
<tr>
<td>UPDRS</td>
<td>Unified Parkinson’s Disease Rating Scale</td>
</tr>
</tbody>
</table>
List of Figures

Figure 1  Sensorimotor Integration and Multisensory Integration ............................. 6

Figure 2 Motor Evoked Potentials and Short- and Long- Latency Afferent Inhibition .... 11

Figure 3 Subregions in the Posterior Parietal Cortex ............................................. 20

Figure 4 TMS studies with Paired-pulse approach with Two Coils .............................. 23

Figure 5 Rubber Hand Illusion .................................................................................. 26

Figure 6 Experimental Set-up and Design .................................................................. 45

Figure 7 Stimulation of PPC with TMS ....................................................................... 47

Figure 8 Behavioural Results ..................................................................................... 51

Figure 8 Modulations of Short- and Long-Latency Afferent Inhibitions by RHI .... 54

Figure 9 RHI and PPC-M1 Interactions ..................................................................... 57

Figure 11 Behavioral Results in PD patients and HCs ................................................. 79

Figure 12 Modulation of Short-latency Afferent Inhibition in PD patients and HCs ... 81

Figure 13 Modulation of Long-latency Afferent Inhibition in PD patients and HCs .... 84

Figure 14 Modulation of PPC-M1 interactions by RHI .............................................. 88

Figure 15 Correlations between RHI Strength and PPC-M1 interactions ................. 91
List of Tables

Table 1 Patients demographic Characteristics ................................................................. 76
1 LITERATURE REVIEW

1.1 Parkinson’s Disease (PD)

1.1.1 Parkinson’s disease and its motor symptoms

Parkinson’s disease (PD) is the second most common neurodegenerative disorder after Alzheimer disease (S. Fahn, Przedborski, Serge, 2009). The cardinal sign of PD is motor dysfunction. Symptomology includes slowness of movements (bradykinesia), increased muscle tone (rigidity), tremor, loss of postural reflexes, flexed posture, and freezing of gait. These motor dysfunctions often lead to difficulties in executing goal-directed actions such as locomotion and fine motor movements with hands. For instance, patients with PD can have a slowness of movement (bradykinesia), reduction in the size of movements (hypokinesia), and difficulties in movement initiation (i.e., freezing). As the disease progresses, patients with PD have neurological deficits that impair cognition, affect, and motor function, and are often left with disabilities making them dependent on others for activities of daily living.

The pathological hallmark of PD is degeneration of the nigrostriatal dopaminergic neurons. This results in striatal dopamine depletion, and abnormal protein inclusions known as Lewy bodies are found in many of the surviving neurons. By the time the motor symptoms appear, about 60% of the dopaminergic neurons in the substantia nigra are lost and a decrease of about 80% of the dopaminergic content in the striatum occurs (S. Fahn, Przedborski, Serge, 2009). Although the pathophysiology of PD is not fully understood, it is widely accepted that it primarily involves disruption of the basal ganglia-motor cortex circuits (Wichmann & DeLong, 2013).

The current treatments of PD are mainly aimed at controlling the motor symptoms. Pharmacotherapy with dopamine precursors or dopamine agonists is the main basis of
the treatment. When the disease advances, surgical treatments, usually deep brain stimulation (DBS), may be considered. Although, these pharmacological and surgical therapies are the main strategies for PD treatment, physiotherapy (PT) and physical exercise are also important for managing the motor symptoms in PD.

1.1.2 Sensory Symptoms and Sensory Impairments in Parkinson’s disease

Although the motor symptoms are often considered as the predominant symptoms of PD and used to diagnose the disease, many PD patients experience non-motor symptoms such as sensory impairments (S. Fahn, Jankovic, & Hallett, 2011).

Decreased sense of smell, hyposmia, can be detected in more than half of PD patients and often precedes the onset of the motor symptoms (S. Fahn et al., 2011). Pain in the initially affected limb may also be one of the first PD symptoms and is often relieved by dopaminergic medications (S. Fahn et al., 2011). Specific sensory symptoms such as pain, numbness, tingling or burning sensations are also reported in about 63% of PD patients (Shulman, Taback, Bean, & Weiner, 2001). These abnormal sensations can result from PD, but in some patients, are induced by dopaminergic therapy (S. Fahn et al., 2011).

Routine clinical examinations of the sensory systems in PD patients are usually normal. However, several experimental studies have revealed abnormal somatosensory perceptions in PD patients.

Tactile perception is compromised in PD patients. Deficits in somatosensory tactile perceptions in the larynx and airway are seen and can contribute to speech or swallowing problems in PD patients (Conte, Khan, Defazio, Rothwell, & Berardelli, 2013). Higher levels of tactile sensory perceptions such as spatial and temporal discriminations are also impaired in PD patients (Fiorio et al., 2007; Sathian, Zangaladze, Green, Vitek, & DeLong, 1997; Zia, Cody, & O'Boyle, 2003). For example, tactile spatial acuity (discrimination) of grating orientation decreases in PD patients.
(Sathian et al., 1997; Shin, Kang, & Sohn, 2005). Dopaminergic medications improve this impairment (Shin et al., 2005). Many studies in PD patients have demonstrated increased somatosensory temporal discrimination threshold (STDT), which can be normalized or decreased by dopaminergic medications (Artieda, Pastor, Lacruz, & Obeso, 1992; Conte et al., 2010; Fiorio et al., 2007; Lee, Kim, & Lyoo, 2005; Rocchi et al., 2013). Proprioception, which refers to the ability to perceive movements or orientations of own limbs/body parts, is another type of somatosensory perception that can be abnormal in PD. Abnormalities in proprioception in PD patients are usually presented as abnormal kinesthesia, and defined more specifically as conscious awareness of position, motion and orientation of own limb or body part in space evoked by movements (Conte et al., 2013). Several studies show that proprioception without the visual feedback was deteriorated more in PD patients than healthy controls (Flash, Inzelberg, Schechtman, & Korczyn, 1992; Jobst, Melnick, Byl, Dowling, & Aminoff, 1997; Konczak et al., 2009; Maschke, Gomez, Tuite, & Konczak, 2003; Zia, Cody, & O'Boyle, 2000). Specifically, patients with PD showed significantly larger errors compared to healthy controls (HC) when verbally reporting the sensed arm position without vision for passive and active arm movements (Zia, Cody, & O'Boyle, 2002). Other studies using joint-angle matching tests showed that PD patients had decreased sensitivity to sense limb position either passively or actively when vision is occluded (Maschke et al., 2003; O'Suilleabhain, Bullard, & Dewey, 2001; Zia et al., 2000). Several studies reported that the sense of own arm motion was abnormal in PD patients (Konczak, Krawczewski, Tuite, & Maschke, 2007; Maschke et al., 2003; Maschke, Tuite, Pickett, Wächter, & Konczak, 2005). Dopaminergic medications are thought to worsen proprioceptive deficits. For instance, PD patients in the OFF-medication state show a worsening of their elbow proprioception after taking dopaminergic medications (O'Suilleabhain et al., 2001). Similarly, PD patients on dopaminergic medications showed greater errors in placing their own hand in a remembered position in space compared to age-matched HC or PD patients in OFF-medication state (Wagle Shukla et al., 2013). Several studies examined the effect of DBS on proprioceptive deficits in PD patients. Subthalamic nucleus DBS (STN-DBS) reversed the proprioceptive deficits in
PD patients (Maschke et al., 2005; Wagle Shukla et al., 2013), suggesting that the basal ganglia are involved in proprioceptive processing.

Although the dopaminergic neurons in the basal ganglia seem to be involved in abnormal sensory processing in PD patients, why these deficits in tactile, or proprioceptive perceptions occur in PD remains unclear. To understand the somatosensory deficits in PD patients, further knowledge of how sensory inputs are utilized to guide accurate motor controls is required. The deficits in sensory system in PD not only lead to the sensory symptoms but could also be related to the motor symptoms. Indeed, the proprioceptive and kinaesthetic impairments seem to be involved in the motor dysfunction as evidenced by significant a correlation between the severity of the motor symptoms and the proprioceptive impairments (Maschke et al., 2003). The following sections will review the abnormal interaction between the sensory and the motor systems in PD.

1.1.3 Deficits in Sensorimotor Integration in Parkinson’s Disease

The motor system in the brain closely links with the sensory system because planning and executing accurate voluntary movements depend crucially on inputs from the sensory system. The sensory system transforms the sensory inputs into motor outputs (Figure 1). This process is known as sensorimotor integration and plays an important role in motor planning and executions (Kandel, Schwartz, Jessell, Siegelbaum, & Hudspeth, 2013; Stone & Gonzalez, 2015). Various types of sensory information such as vision, tactile, auditory perceptions or proprioception can converge with motor outputs through visuo-motor integration, tactile-motor integration, audio-motor integration or proprioceptive-motor integration, respectively.

Research in sensorimotor integration in PD has led to the suggestion that sensory impairments and defective sensorimotor integration can result in motor symptoms and decreased motor performances. Behavioural or kinematic studies that examined sensorimotor integration in PD patients have demonstrated failures of integration of
sensory inputs with motor program at the behavioural level (Adamovich, Berkinblit, Hening, Sage, & Poizner, 2001; Demirci, Grill, McShane, & Hallett, 1997; Flash et al., 1992; Jobst et al., 1997; Rickards & Cody, 1997).

Proprioceptive-motor integration deficits are found in PD (Flash et al., 1992; Jobst et al., 1997; Rickards & Cody, 1997). For instance, PD patients are less susceptible to muscle vibration-induced movement errors that are normally observed in HC (Rickards & Cody, 1997). In fact, the defective proprioceptive-motor integration in PD patients leads to an over-reliance on visual inputs (Flash et al., 1992; Jobst et al., 1997).

Tactile-motor integration in PD patients may also be affected. A study reported impaired tactile-motor integration in PD patients during an object-shape-recognition test with active exploratory movements (B. J. Weder et al., 1999). However, other studies have suggested that tactile stimuli are equally beneficial on motor performance in PD patients compared to HC. PD patients show normal accuracy when using tactile information to reach-to-point at a target on the skin with the contralateral arm (Jobst et al., 1997). In a tactile precision grip task, in which participants are required to use tactile feedback to control grip force, both PD patients and HC successfully increased the grip force when the objects were slippery (Ingvarsson, Gordon, & Forssberg, 1997). These results indicate normal tactile-motor integration in PD.

The inconsistency of the sensorimotor integration in PD patients at the behavioural level may arise from the complex physiology of sensorimotor integration process. To design appropriate experiments to address whether sensorimotor integration is defective in PD patients, it is necessary to understand the pathophysiology of sensorimotor integration.
Figure 1  Sensorimotor Integration and Multisensory Integration

Sensorimotor integration involves the conversion of sensory inputs into motor outputs. Multisensory integration, which involves combining sensory inputs from different modalities such as tactile, proprioceptive and visual inputs, can modulate motor responses through sensorimotor integration. As each sensory input is encoded in a different reference frame, multisensory integration areas such as premotor or posterior parietal cortices transform the sensory inputs into a common reference frame, which are then combined in the motor system. M1: primary motor cortex, S1: primary somatosensory cortex, V1: primary visual cortex.
1.2 Physiology and Pathophysiology of Sensorimotor Integration

1.2.1 Neurophysiology of Sensorimotor Integration in Healthy Populations

Sensorimotor integration has been observed in vast areas in the brain including basal ganglia (Hall, 2008; McFarland & Haber, 2000; Reig & Silberberg, 2014), thalamus (Hirashima & Yokota, 1997; McFarland & Haber, 2000), cerebral cortices (Chen, Corwell, & Hallett, 1999; Pfurtscheller, Stancák, & Neuper, 1996; Salenius, Schnitzler, Salmelin, Jousmäki, & Hari, 1997; Salmelin & Hari, 1994), cerebellum (Proville et al., 2014) and the superior colliculus in the brainstem (Doubell, Skaliora, Baron, & King, 2003). The basal ganglia receive inputs from cortical areas including sensory areas and project back to a wide range of cortical areas including motor areas via the thalamus (Hall, 2008). Thus, the basal ganglia as well as the thalamus allow sensorimotor integration using the basal ganglia-motor cortical circuits. Synaptic convergence of inputs from the primary motor cortex with inputs from sensory cortex has been found in striatum of rats, suggesting an anatomical substrate of sensorimotor integration in the basal ganglia.

Cortico-spinal pathway also contributes to sensorimotor integration. Electrophysiological studies with healthy human subjects have shown that electrical stimuli to peripheral nerves modulate the excitability of the corticospinal motor neurons (Chen et al., 1999; Hirashima & Yokota, 1997). Depending on the timing of the nerve stimulation, the cortico-spinal motor neurons may be facilitated or inhibited. Magnetoencephalographic (MEG) and electroencephalographic (EEG) studies suggest that sensorimotor integration occurs at cortical level. They showed that peripheral nerve stimulation induced immediate suppression of rhythmic oscillation followed by increased activity in
the primary motor cortex (Chen et al., 1999; Pfurtscheller et al., 1996; Salenius et al., 1997; Salmelin & Hari, 1994).

1.2.2 The Use of Transcranial Magnetic Stimulation (TMS) to Assess Sensorimotor Integration

1.2.2.1 Transcranial Magnetic Stimulation (TMS)

Transcranial magnetic stimulation (TMS) is a technique to focally stimulate the brain non-invasively and painlessly from the scalp (Rothwell, 1997). The stimulator consists of a large capacitor and a stimulation coil. The stimulator delivers electrical currents, which produce transient magnetic fields lasting approximately 200 µs. The magnetic field penetrates the scalp and the skull, and reaches the cerebral cortex usually 1-2 cm below the scalp. The intensity of magnetic field decreases rapidly with distance from the coil, and it is likely that the magnetic field activates neural elements at the surface of the cerebral cortices (Wassermann et al., 2011). TMS likely activates axons rather than the cell bodies or the initial segments of neurons (Barker, Garnham, & Freeston, 1991; Rothwell, 2011). As different neuronal populations have different activation thresholds, the intensity of the stimuli determines which neuronal populations will be activated (Rothwell, 2011).

The magnetic stimulations of the primary motor cortex (M1) can evoke electromyographic (EMG) responses in the contralateral muscles, termed motor evoked potentials (MEPs) (Figure2). Comparing the responses from different coil orientations, the largest MEPs are produced when the coil is held to induce currents in the posterior-anterior (PA) direction, and approximately perpendicular to the central sulcus (Hallett, 2007). MEP recordings are widely used to assess motor cortical excitabilities in healthy subjects and in patients with impairment in the central nervous system (Rosler & Magistris, 2011). The modulation of the MEP amplitude size after a single-pulse TMS to M1 reflects the excitability of the both cortical and spinal motor neurons (Abbruzzese & Trompetto, 2002). The modulation before and after a task can be used to assess the
change in the cortical excitability by the task if the excitability of the spinal motor neurons is unchanged.

1.2.2.2 Short-latency Afferent Inhibition (SAI) and Long-latency Afferent Inhibition (LAI) in Healthy Populations

The modulation of cortical excitability in M1 by peripheral nerve stimulation can be measured by pairing the peripheral nerve stimulation with TMS to M1 (Figure 2). TMS to M1 after median nerve stimulation (MNS) at the wrist or digital nerve stimulation (DNS) decreases MEP amplitudes, suggesting an inhibitory effect of electrical nerve stimulation (Chen et al., 1999; Ni et al., 2011; Sailer et al., 2003; Tokimura et al., 2000). The inhibitory effect depends on the inter-stimulus intervals (ISIs) between the median or digital nerve stimulation and TMS to M1 (Chen et al., 1999; Devanne et al., 2009; Ni et al., 2011; Tokimura et al., 2000). The inhibition is greatest when nerve stimulation is three times the individual’s sensory threshold (ST). Interestingly, inhibition does not increase with higher nerve stimulation intensities once the intensity reaches three times of ST (Cash, Isayama, Gunraj, Ni, & Chen, 2015; Chen et al., 1999; Ni et al., 2011).

M1 inhibition that occurs approximately 20ms after MNS is known as short-latency afferent inhibition (SAI). SAI likely occurs at the cortical level because direct recordings from patients with implanted cervical epidural electrodes show that the later corticospinal waves (Indirect or I waves) were suppressed by the MNS (Tokimura et al., 2000). Considering that approximately 20ms is required for peripheral stimuli to arrive at the primary somatosensory cortex (S1) as indicated by the N20 wave of somatosensory evoked potentials (SEPs) from MNS, SAI likely reflects the direct interaction between S1 and M1 (Sailer et al., 2003). Indeed, it has been shown that M1 receives mono-synaptic inputs from S1 in rodents (Rocco-Donovan, Ramos, Giraldo, & Brumberg, 2011), suggesting that SAI may reflect the mono-synaptic inputs (Cash et al., 2015).

Long-latency afferent inhibition (LAI) occurs when the MNS is delivered about 200ms before TMS to M1 (Chen et al., 1999; Sailer et al., 2003). The mechanism of LAI
remains unclear. However, the finding that LAI was not influenced by dopaminergic medications suggests that LAI may involve sensorimotor integration in cortical association areas (Sailer et al., 2003).

SAI and LAI are well-established parameters to measure tactile sensorimotor integration in healthy subjects (Lapole & Tindel, 2015; Wood, Gallese, & Cattaneo, 2010) as well as patients with neurological disorders such as PD (Sailer et al., 2007; Sailer et al., 2003; Wagle Shukla et al., 2013), dystonia (Abbruzzese, Marchese, Buccolieri, Gasparetto, & Trompetto, 2001; Kessler, Ruge, Ilić, & Ziemann, 2005; Pirio Richardson, Bliem, Voller, Dang, & Hallett, 2009; Richardson et al., 2008), restless leg syndrome (RLS) (Rizzo et al., 2010) and Tourette syndrome (Orth & Rothwell, 2009).
Figure 2 Motor Evoked Potentials and Short- and Long- Latency Afferent Inhibition

Pairing peripheral nerve stimulation with transcranial stimulation (TMS) to the primary motor cortex (M1) and comparing the amplitude of motor evoked potentials (MEPs) enable us to measure how the peripheral nerve stimulation modulates the cortical excitability of M1. If the ratio of the conditioned (with peripheral/digital nerve stimulation) to the unconditioned (test TMS alone to M1) MEP amplitudes exceeds 1, it indicates facilitatory influence of the peripheral nerve stimulation on M1 excitability. In contrast, the ratio below 1 indicates inhibitory influence of the nerve stimulation.
### 1.2.2.3 Short-latency Afferent Inhibition (SAI) and Long-latency Afferent Inhibition (LAI) in PD Patients

Several studies tested SAI and LAI in PD patients to investigate sensorimotor integration. A study showed reduced LAI in PD patients in the OFF medication state while SAI was normal (Sailer et al., 2003). LAI was also reduced in PD patients ON medications, indicating that dopaminergic medications did not restore the abnormal LAI (Sailer et al., 2003). Interestingly, SAI was reduced with dopaminergic medications but the reduced SAI was restored by STN-DBS (Sailer et al., 2007). LAI was also restored by STN-DBS (Wagle Shukla et al., 2013). The level of SAI in PD patients was found to be correlated with the severity of the motor symptoms, especially bradykinesia, suggesting a possible contribution of the altered sensorimotor integration to the motor symptoms (Tamburin et al., 2003).

Considering the pathological changes occurring in the basal ganglia in PD and the ability of the basal ganglia to integrate sensory inputs with motor outputs, the basal ganglia may mediate the abnormal sensorimotor integration in PD patients. PD patients showed an abnormal reduction of the first inhibitory component of EMG activities in a cutaneous reflex study and the reduced inhibition was restored by dopaminergic medications (Fuhr, Zeffiro, & Hallett, 1992). The normalization of the reduced cutaneous reflex response by dopaminergic medications and the restoration of SAI and LAI by STN-DBS (Sailer et al., 2007; Wagle Shukla et al., 2013) may suggest involvement of the basal ganglia circuits in sensorimotor integration. However, because SAI was normal in PD OFF medication and reduced LAI was not restored by dopaminergic medications, the altered sensorimotor integration can also be mediated by non-dopaminergic pathways such as cortical areas.

Because SAI likely reflects direct interaction between S1 and M1, normal SAI in PD OFF medication and reduced SAI in PD ON medication likely represents negative dopaminergic influence over sensory cortical areas, especially S1. The reduced SAI was seen in the more affected side but not in the less affected side, suggesting that the deficits in SAI in PD patients ON medication occur in more advanced PD (Sailer et al., 2003).
Given that dopaminergic medication influences proprioception (O’Suilleabhain et al., 2001), it is possible that the processing of cutaneous or muscle afferent information can be also influenced. Intracortical circuits within S1 show that perception of sensory stimuli induced by paired-pulse TMS over S1 was modulated in healthy subjects and that this modulation was abnormal in PD patients with dopaminergic medications compared to HC. PD patients in the OFF medication state did not differ from HC (Palomar et al., 2011). The result suggests dopaminergic influence in S1 in PD patients, consistent with functional Magnetic Resonance Imaging (fMRI) data showing decreased activity in somatosensory and motor regions in PD patients during passive tactile and movement tasks (Zhao et al., 2014).

Reduced LAI in PD patients regardless of dopaminergic medication states is most likely related to structures involved in sensory processing other than S1 because SAI in PD OFF medication state was not different from HC. Although the pathway involving LAI remains unclear, the LAI deficit in PD patients may involve cortical sensory processing areas rather than basal ganglia pathways because it was not normalized by dopaminergic medications (Sailer et al., 2003). Previous studies have demonstrated depressed SEPs and proprioception-related potentials in PD (Abbruzzese & Berardelli, 2003; Seiss, Praamstra, Hesse, & Rickards, 2003). SEPs in PD patients were reduced in the frontal and parietal areas (Bostantjopoulou et al., 2000; Pierantozzi et al., 1999; Rossini et al., 1993). These findings support the involvement of the frontal (Abbruzzese & Berardelli, 2003) and parietal (S1 or secondary sensory cortex: S2) (Seiss et al., 2003) areas in the abnormal sensory processing in PD patients. Reduced LAI may involve abnormal cortical activations in the frontal-parietal areas. Several neuroimaging studies have also shown abnormal cortical activation related to somatosensory processing in PD. A positron emission tomography (PET) study showed an abnormal pattern of somatosensory processing at the cortical level (Boecker et al., 1999). Sensory stimulation results in increased activation of ipsilateral associative sensory areas (S2 and insular cortex), and reduced activation in contralateral sensorimotor and promoter cortices, S2 and posterior cingulate cortex in PD patients compared to HC (Boecker et al., 1999). Over-activated bilateral prefrontal regions in PD patients are found with fMRI
during a tactile-motor integration, possibly reflecting a compensatory mechanism (Zhao et al., 2014). Importantly, these studies indicate the involvement of multiple cortical areas in the abnormal sensorimotor integration.

1.3 Multisensory Integration

1.3.1 Multisensory Sensory Integration and Sensorimotor Integration in Healthy Populations

Healthy individuals often rely on multiple sensory inputs to perceive the environment more accurately rather than depending on unimodal sensory information (Amedi, Malach, Hendler, Peled, & Zohary, 2001; Buelte et al., 2008; Kayser & Logothetis, 2007). This interaction between sensory inputs from different modalities is termed multisensory integration (Ernst & Bülthoff, 2004). When multisensory information from different sensory modalities is in different units, or coordinates, it has to be transformed into the same units and coordinates and then, integrated into a coherent multisensory percept (Ernst & Bülthoff, 2004). Previous studies suggest that multisensory integration can modulate perception. Depending on the context, multisensory integration increases or decreases sensitivity to subtle stimuli in one sensory modality, resulting in perceptual changes (Kayser & Logothetis, 2007; Mahoney, Wang, Dumas, & Holtzer, 2014; Pavani, Spence, & Driver, 2000). Multisensory integration can also influence motor responses. Planning and executing an action requires an integration of vision, proprioception, audition, and tactile perception to provide a perceptual representation of the external world (Figure 1). When audio cue is combined with visual cue to a motor response, the motor response is facilitated in healthy individuals due to modulation of the motor response by multisensory integration (visuo-auditory facilitation) (Fearon, Butler, Newman, Lynch, & Reilly, 2015). Whether the motor response is facilitated or inhibited also depends on the context (Fearon et al., 2015; Hershenson, 1962; Kanayama, Sato, & Ohira, 2007; Kayser & Logothetis, 2007). Multisensory integration plays an important role in sensorimotor integration. Because sensory information is
initially encoded relative to the characteristics of the individual sensory receptor system, it needs to be integrated and transformed into a common reference frame (Giummarra, Gibson, Georgiou-Karistianis, & Bradshaw, 2008) to construct a coherent perceptual representation in the brain. This representation is then transformed into motor outputs for appropriate action.

How multisensory integration modifies perception or motor response in healthy individuals remains unclear because there are few neurophysiological investigations on the influence of multisensory integration on the sensory and motor systems. The modification of perceptions or motor responses by multisensory integration may be related to the efficiency of sensory processing of each modality during multisensory integration. Recent computational research proposes that there is flexible weighting of different sensory modalities during multisensory integration. Sensory signals are weighted in each context and this weighting is flexible in order to minimize errors resulting from noisy signals and to improve sensorimotor performance (Sober & Sabes, 2005). Further studies are required to test this computational model.
1.3.2 Neural Correlates of Multisensory Integration

Historically, physiological studies of multisensory integration focused primarily on identifying structures that show responses to more than one sensory modality. Parietal, temporal and frontal cortical regions of primates have been reported to respond to multisensory inputs (Rizzolatti, Cattaneo, Fabbri-Destro, & Rozzi, 2014). A human fMRI study revealed areas in the premotor and the posterior parietal cortices that respond to both visual and tactile stimuli to specific body parts (Bremmer et al., 2001). These areas are distributed across wide areas of association cortices which include posterior parietal cortex (PPC), ventral premotor cortex (PMv), lateral occipital cortex (LOC) in occipito-temporal region and superior temporal sulcus (STS). Electrophysiological studies in monkeys have shown that neurons in the premotor area and PPC, particularly areas within the inferior parietal lobe and the ventral intraparietal sulcus (IPS) respond to both visual and tactile stimuli (Graziano, 2001; Rizzolatti, Fadiga, Fogassi, & Gallese, 1997). IPS in the PPC and the LOC become active during visual-haptic object shape recognition task (Amedi et al., 2001; Lacey & Sathian, 2012), suggesting that these areas mediate visuo-tactile integration. Neurons in PMv and STS respond to somatosensory, auditory and visual signals (Cappe, Rouiller, & Barone, 2012).

In addition to these areas within the association cortices, few studies have reported that low-level sensory cortical areas such as primary somatosensory cortex (S1), thalamus, putamen, and superior colliculus in the brain stem may also contribute to multisensory integration (Cappe et al., 2012; C. Cappe, E. M. Rouiller, & P. Barone, 2012; Graziano, 2001; Rizzolatti, Fadiga, et al., 1997). The thalamus interconnects with cortical areas including PPC and premotor cortical areas and may be involved in multisensory integration. S1 is originally thought to be a purely somatosensory area. However, monkey studies reveal a direct connection between S1 and visual cortical areas (Cappe et al., 2012) and visual responsiveness in parts of S1 (Iwamura, 1998; Lacey & Sathian, 2012), suggesting that S1 plays a role in multisensory integration. Interestingly, some of the connections were restricted to the representations of certain body parts (Cappe &
Barone, 2005), suggesting the importance of multisensory integration for perception of body parts. This topic will be covered in a later section (section 1.3.5).

1.3.3 The Role of Posterior Parietal Cortex in Multisensory Integration and Sensorimotor Integration

Fronto-parietal association areas such as the premotor cortex and posterior PPC play an important role in the planning and control of goal-directed movements (Koch, Fernandez Del Olmo, et al., 2008; Petrides & Pandya, 1984; Vesia & Crawford, 2012). These areas have been shown to respond to multisensory stimuli as well as being a critical hub sub-serving specific motor functions (Brozzoli, Makin, Cardinali, Holmes, & Farne, 2012). This network is thought to provide an interface between perception and action. Goal-directed movements are mediated by PPC neurons, which receive inputs from the early visual or somatosensory areas and are interconnected with the premotor cortex (Koch et al., 2007; Petrides & Pandya, 1984; Rizzolatti, Fogassi, & Gallese, 1997; Vesia & Crawford, 2012). The premotor cortex directly projects to M1 with access to the control of upper limb movements (Davare, Montague, Olivier, Rothwell, & Lemon, 2009; Graziano & Gross, 1998; Koch, Fernandez Del Olmo, et al., 2008). Monkey studies show that PPC is active during the preparation of specific movements involving the hand (Andersen, 1997; Graziano & Gross, 1998).

The PPC can be subdivided into several functionally specialized subregions (Figure 3). Area 5 in the superior parietal lobe (SPL) predominantly receives tactile and proprioceptive inputs from S1 and S2 (Sakata, Takaoka, Kawarasaki, & Shibutani, 1973). An electrophysiological study showed that some neurons in the area also responded to certain visual stimuli (Sakata et al., 1973). These multisensory inputs converge with neurons in Brodmann area 5 in SPL (Sakata et al., 1973), which codes the location or the posture of arm relative to the other body parts (Andersen, 1997; Gentile, Petkova, & Ehrsson, 2011; Lewis et al., 2011) and creates a holistic concept of the body image by transforming the sensory inputs into a common coordinate system.
SPL is also known to send intra-hemispheric inputs to the arm and hand representations in the M1 in human (Andersen, 1995; Andersen & Buneo, 2002; Premji, Rai, & Nelson, 2011; Ziluk, Premji, & Nelson, 2010) and non-human primates (Petrides & Pandya, 1984). Fibers from SPL also project to other frontal areas such as dorsal premotor cortex (PMd) and supplementary motor area (SMA) (Makris et al., 2005; Petrides & Pandya, 1984). A lesion in SPL causes both motor and sensory deficits due to inability to maintain internal representations of objects and own body parts (Wolpert, Goodbody, & Husain, 1998). Thus, SPL is critical in sensory-motor transformations and coding of spatial location of objects with the arms (Crammond & Kalaska, 1989; Granek, Pisella, Blangero, Rossetti, & Sergio, 2012; Hawkins, Sayegh, Yan, Crawford, & Sergio, 2013; Kalaska, 1996; Kalaska, Caminiti, & Georgopoulos, 1983; Reed, Klatzky, & Halgren, 2005; Sakata et al., 1973).

The inferior parietal lobe (IPL) is another subregion of the PPC which has multiple functions such as processing information for perceptual body judgement (Kammers, Verhagen, et al., 2009) and recognising an object with the hand (Reed et al., 2005). IPL receives indirect influences of somatosensory inputs from other areas in PPC such as SPL and visual regions to facilitate multisensory integration.

Areas within the intra-parietal sulcus (IPS), the sulcus between SPL and IPL, dominate visuo-motor integration. Several monkey studies have revealed that a part of the IPS is active during preparation of reaching, grasping, and eye movements (Andersen, 1997; Graziano & Gross, 1998). The area transforms stimuli in peripersonal space, the space within an arm’s reach, into a hand-centered representation, therefore informing the spatial position of target objects with respect to the hand position (Graziano & Gross, 1998; Vesia & Crawford, 2012). The anterior part of the IPS (aIPS) is specialized for grasping (Begliomini, Wall, Smith, & Castiello, 2007), while the medial part of the IPS (mIPS) is involved in reaching (Vesia & Crawford, 2012). Virtual lesions induced by TMS to the aIPS disrupts ongoing movements (Franklin & Wolpert, 2011; Tunik, Frey, & Grafton, 2005; Wolpert et al., 1998).
The superior parieto-occipital cortex (SPOC) is located in medial posterior part of PPC. This area selectively encodes reaching and pointing actions to peripheral locations (Vesia & Crawford, 2012). It is also strongly activated by viewing tools in personal space (Vesia & Crawford, 2012). Repetitive TMS to SPOC resulted in deviation of reaching, suggesting that sensorimotor integration relating to arm involves SPOC (Vesia, Prime, Yan, Sergio, & Crawford, 2010).

Thus, PPC allows functional interactions between the sensory and the motor system and plays an important role in multisensory integration.
Figure 3: The posterior parietal cortex (PPC) can be subdivided into several functionally specialized subregions. SPL: the superior parietal lobe, IPL: the inferior parietal lobe, SPOC: the superior parieto-occipital cortex, aIPS: the anterior part of the intra-parietal sulcus (IPS), mIPS: the medial part of the IPS, and cIPS: the caudal part of the IPS. CS: the central sulcus.
1.3.4 Functional Interactions between the Left Posterior Parietal Cortex (PPC) and Ipsilateral Primary Motor Cortex (M1) Examined by Transcranial Magnetic Stimulation (TMS)

Functional imaging studies have shown the involvement of fronto-parietal network including the premotor and the posterior parietal cortices in goal-directed action (Culham & Valyear, 2006). However, functional interactions between two different areas and the time course of the interaction can be better probed by studies with paired-pulse TMS paradigm with two coils, which detects inputs from other cortical areas to M1 (Koch & Rothwell, 2009; Rothwell, 2011). The paired-pulse TMS paradigm involves a conditioning TMS pulse (conditioning stimulus, CS) to a cortical region of interest followed by TMS to M1 (test stimulus, TS) with a few ms interval. The CS activates a putative pathway from the site of interest to M1. The method can probe changes in M1 excitability induced by the CS. If the CS increases the amplitude of the MEP evoked by test stimulus (TS) to M1, it is considered facilitatory, whereas a decrease is thought to have an inhibitory influence over the M1 (Figure 4).

With this approach, interactions between PPC and ipsilateral M1 have been probed (Karabanov, Christensen, Ritterband-Rosenbaum, Siebner, & Nielsen, 2014; Koch et al., 2007; Koch, Ribolsi, et al., 2008; Vesia, Bolton, Mochizuki, & Staines, 2013). Whether PPC has facilitatory or inhibitory influence over M1 depends on several factors including the CS intensity, the ISIs between CS and TS and the specific areas targeted within PPC (Karabanov et al., 2014; Koch et al., 2007; Koch, Ribolsi, et al., 2008; Vesia et al., 2013; Ziluk et al., 2010).

SPL is essential to representing maintained postures and receives proprioceptive inputs from primary and secondary somatosensory areas. A TMS study reported that SPL-M1 interactions were neither inhibitory or facilitatory at rest while SPL facilitated M1 excitability during application of vibratory tactile inputs from a digit (Ziluk et al., 2010).

Other TMS studies with paired-pulse TMS approach targeted IPL (Koch, Ribolsi, et al., 2008). At rest, the CS facilitated M1 excitability to the caudal intra parietal sulcus (cIPS).
at 90% of resting motor threshold. There were two phases of facilitation with peaks at 4 ms and 15 ms after cIPS stimulation. Stimulation of the aIPS at the same intensity inhibited the M1 excitability. Stimulating mIPS did not influence M1 excitability. Several TMS studies found that aIPS-M1 interaction was facilitated at rest at 4 and 6 ms ISIs (Karabanov et al., 2014; Koch et al., 2007) as well as during motor planning at 4 ms ISI (Vesia et al., 2013). The same study also demonstrated that the interaction between SPOC and M1 at rest was different from during motor planning. At rest, SPOC-M1 interactions did not show either facilitation or inhibition. Interestingly, interaction between SPOC and M1 is facilitated at 4 ms ISI during motor planning. Thus, PPC-M1 interactions are strongly influenced by the subdivisions of PPC targeted and the cognitive state. Further research using the paired-pulse TMS approach is still required to determine functional interactions between other PPC regions and M1 for other tasks.
Figure 4. With paired-pulse TMS approach with two coils, condition stimulus (CS) is applied to a brain region, with the posterior parietal cortex (PPC) illustrated in this figure, followed by test stimulus (TS) to the primary motor cortex (M1). The ratio of the conditioned (CS+TS) to the unconditioned (TS alone) less than 1 indicates inhibitory, and more than 1 indicates facilitatory influences of PPC over M1.
1.3.5 Rubber Hand Illusion as a Tool to Investigate Multisensory Integration

1.3.5.1 Behavioral Studies of Rubber Hand Illusion

As mentioned in the previous section (1.3.2), multisensory integration is strongly associated with perception of one’s own body parts. Goal-directed movements require the identification of one’s own body parts, which involves informing the brain what parts belong to the body (ownership of a body part) and where those parts are currently located (localization of a body part) (Berlucchi & Aglioti, 2010) to construct the representation of one’s own body in the brain. The representation of one’s own body involves encoding and integrating a wide range of multisensory inputs, primarily visual, tactile, and proprioceptive inputs (Aspell, Lenggenhager, & Blanke, 2012; Aspell, Palluel, & Blanke, 2012). The update of mental representations of our body is necessary for determining what motor commands are needed to achieve a desired movement by calculating motor outputs from sensory inputs. It is also important for anticipating future sensory inputs as the result of the motor command currently being held in the brain (Franklin & Wolpert, 2011; T. Heed, Roder, Brigitte, 2012; Kandel et al., 2013; Wolpert, Ghahramani, & Jordan, 1995). Because body postures constantly change with actions, the brain needs to align tactile coordinates precisely to proprioceptive information, both of which should also be matched with visual inputs. The spatial locations constituted of the different sensory modalities are transformed into a common reference system through multisensory integration to create a coherent and consistent body representation (J. E. Aspell et al., 2012). In other words, creating a mental representation of our own body requires multisensory integration (Rizzolatti et al., 2014; Stone & Gonzalez, 2015).

The body representation in the brain formed by the process of multisensory integration can be examined and modulated by an experimental procedure known as the “rubber hand illusion (RHI).” Since its first report by Botvinick and Cohen (Botvinick & Cohen, 1998), the RHI has been widely used to evoke and assess visuo-tactile-proprioceptive
multisensory integration at the behavioural level (Armel & Ramachandran, 2003; Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Ehrsson, Holmes, & Passingham, 2005; Tsakiris & Haggard, 2005). In RHI experiment, participants view an artificial rubber hand being stroked with a brush while his or her real hand is visually occluded and is simultaneously stroked with another brush (Figure 5). When the timing of the brush strokes is synchronized, the participants perceives the touch of the brush stroking the rubber hand but not of their own hidden hand, as if the rubber hand is a part of one’s own body (Botvinick & Cohen, 1998). In addition to the ownership feeling of the rubber hand, the participants also demonstrate shifts in the perceived position of their own hand and arm towards the rubber hand, suggesting a shift of proprioception. The ownership feeling of the rubber hand and the shift in the perceived hand position is reduced when the two brushes asynchronously stroke the hands (Botvinick & Cohen, 1998; Makin, Holmes, & Ehrsson, 2008). To evoke RHI, there must be a congruency among the different sensory modalities. Visual capture of body postures can be used to calibrate the spatial relationship among the different modes of sensory inputs, and the brain weighs the different sensory inputs depending on their reliabilities (J. E. Aspell et al., 2012). The relative weighting function of RHI will be discussed in the next section.
Figure 5 Rubber Hand Illusion

Figure 5 shows the rubber hand illusion (RHI) set-up. A participant sat at a table putting his or her own hand on it. Medial to the own hand, an artificial rubber hand was placed in a way that it appears to be coming out of his or her body. A partition was placed between the subject’s own hand and the rubber hand, so that the own hand was occluded from his or her vision. The two hands were simultaneously being stroked by two separate paintbrushes while the participant was attending to the rubber hand.
1.3.5.2 The Role of Cognitive Process during RHI

Although multisensory integration is essential to establish RHI, a cognitive component is also required for this process. During the cognitive process of RHI, the hand representation is matched with pre-stored information about the own corresponding body part (internal representation). Some RHI experiments have shown that RHI does not occur if the rubber hand is placed in anatomically incongruent position or substituted by a non-corporeal object (Longo, Schüür, Kammers, Tsakiris, & Haggard, 2008; Tsakiris, 2010). Therefore, the brain distinguishes what can and what cannot be incorporated into one’s own body representations (Tsakiris & Haggard, 2005). If the incoming visual inputs are sufficiently matched with the pre-existing body image, then multisensory inputs will be matched for synchronicity and the integration occurs (Kilteni, Maselli, Kording, & Slater, 2015; Tsakiris, 2010).

Cognitive processes also influence weighting of different sensory modalities during the multisensory integration. Unlike the natural circumstance of self-body perception, the RHI experiment creates conflicts between vision, tactile and proprioception. It is known that when sensory inputs derived from different modalities are experimentally placed in a conflict, for example by mismatching vision of the mouth and audition of a person speaking, the percept is skewed to something intermediate between the percept of each modality alone (McGurk & MacDonald, 1976). Similarly, during the RHI, the proprioception is compromised to match with visual input, which is supported by synchronized tactile inputs to resolve the conflict (Makin et al., 2008; Tsakiris & Haggard, 2005). Due to this cognitive process, the gain of the incongruent sensory inputs such as proprioception are decreased and the gain of reliable inputs such as vision are increased (Dempsey-Jones & Kritikos, 2014; Makin et al., 2008), resulting in increased relative weighting on visual inputs than somatosensory inputs during multisensory integration. Thus, the RHI experiences arise from the interaction between the cognitive process and the multisensory integration during the process of constructing a coherent body representation in the brain (Makin et al., 2008).
Some behavioral studies suggested that the modulation of sensory gains might result in tactile perception changes as well as proprioceptive modulation. Somatosensory tactile inputs from one’s own hand are suppressed after RHI (Folegatti, de Vignemont, Pavani, Rossetti, & Farnè, 2009; G. L. Moseley et al., 2008; Zopf, Harris, & Williams, 2011). Participants show slower responses to tactile stimuli to their own hand after the RHI (Folegatti et al., 2009). However, the neurophysiological basis of this result has not been investigated.

### 1.3.5.3 RHI influences on Motor Responses

Considering that multisensory integration is closely linked to sensorimotor integration, it is possible that RHI influences motor responses. RHI induces multisensory integration and modulates motor performance (T. Heed et al., 2011). Likewise, cortical excitability in M1 decreases after the RHI (Della Gatta et al., 2016) and when participants experienced ownership over a moving hand compared to when they did not feel ownership (Schutz-Bosbach, Avenanti, Aglioti, & Haggard, 2009). However, RHI does not influence kinematic parameters for a ballistic movement (Kammers, de Vignemont, Verhagen, & Dijkerman, 2009; Kammers, van der Ham, & Dijkerman, 2006). Therefore, further investigations and neurophysiological evidence supporting modulation of the motor system by RHI are needed to resolve these discrepancies.

### 1.3.5.4 Application of RHI in Neuropsychiatric Disorders

RHI studies have revealed how multisensory integration is involved in self-body perception in healthy individuals and how this process is impaired in neurological and psychiatric disorders. RHI is abnormal in patients with focal hand dystonia, schizophrenia and autism (Fiorio et al., 2011; Peled, Pressman, Geva, & Modai, 2003; Thakkar, Nichols, McIntosh, & Park, 2011). Patients with schizophrenia show a greater degree of the RHI, evidenced by a stronger rubber hand ownership and greater
proprioceptive arm shift than HCs (Peled et al., 2003; Thakkar et al., 2011). Patients with focal hand dystonia, a movement disorder characterized by sustained or intermittent muscles contraction causing abnormal posture or repetitive movements, show reduced arm shift toward the rubber hand (Fiorio et al., 2011). Given that sensorimotor integration is altered in both focal hand dystonia (Avanzino & Fiorio, 2014) and schizophrenia at the behavioural level (Shergill, Samson, Bays, Frith, & Wolpert, 2005; Velasques et al., 2011), it is likely that RHI may interfere with sensorimotor integration. By corollary, the RHI paradigm can be used to examine diseases where multisensory integration and sensorimotor integration are disrupted.

1.3.5.5 Brain Regions Involving in Multisensory Integration for Own Body and Rubber Hand Illusion

Lesions studies show that multiple brain regions are involved in multisensory integration for self-body perception. Denial of the ownership of own limb using the RHI has been reported in patients with lesions in the premotor area and the parietal lobe (Vallar & Ronchi, 2009; Zeller, Gross, Bartsch, Johansen-Berg, & Classen, 2011). The perception of limb movements likely depends on the primary sensory (S1), motor, and premotor cortices. In contrast, the current body posture is likely represented differently from limb movement perception. Proprioceptive inputs are processed initially in S1 and then S2. Maintenance of a still posture is represented in posterior parietal areas, such as the SPL (J. E. Aspell, B. Lenggenhager, & O. Blanke, 2012; Harris & Wolpert, 1998; Pellijeff, Bonilha, Morgan, McKenzie, & Jackson, 2006).

It is still controversial whether a body representation in motion is different from a still body representation (Gallagher, 1986; Kammers et al., 2006; Preston & Newport, 2011). The body representation in motion is mostly based on proprioception and information from a motor command while the still body representation is derived primarily from visual inputs of own body and a body image constructed from stored memories (Berlucchi & Aglioti, 2010; Schwoebel & Coslett, 2005). However, both types of mental
body representations share multisensory integration networks (T. Heed, Roder, Brigitte, 2012; Rizzolatti, Fogassi, et al., 1997; Serino et al., 2013; Vesia & Crawford, 2012). Therefore, it is likely that these processes interact with each other. Brain regions activated during RHI are similar to regions involved in multisensory integration of the self-body representation (Bremmer et al., 2001; Graziano & Gross, 1998), suggesting multisensory integration during RHI. Evoked potential studies show RHI-related potentials over frontocentral-parietal areas (J. E. Aspell et al., 2012; T. Heed, Roder, Brigitte, 2012; Zeller, Litvak, Friston, & Classen, 2015), supporting the involvement of both somatosensory and multisensory areas of the fronto-parietal cortices in RHI. Many fMRI studies have consistently shown that RHI is associated with the activation of PPC and premotor cortex. The strength of RHI is correlated with the activity in PMv (Ehrsson et al., 2005; Ehrsson, Spence, & Passingham, 2004; Limanowski & Blankenburg, 2015). RHI increases activity in the IPL, particularly in the medial wall of IPS (Ehrsson et al., 2004). Because IPL sends information to PMv (Petrides & Pandya, 1984), the IPL is likely involved in the correlation between PMv activity and the subjective RHI experience. A lesion study in stroke showed that the white matter connecting the parietal and premotor cortices was necessary to induce RHI (Giummarra et al., 2008). In addition, perceptual shift in one’s own hand after RHI was attenuated by inhibiting the IPL with repetitive TMS (Kammers, Verhagen, et al., 2009). However, the subjective RHI experience including ownership feeling was not disrupted by the TMS of IPL (Kammers, Verhagen, et al., 2009). Another study reported that the participants experienced exaggerated ownership even for non-corporeal objects when the right temporo-parietal junction (TPJ) was suppressed by TMS (Serino et al., 2013; Tsakiris, Costantini, & Haggard, 2008). These results indicate that the parietal-premotor multisensory integration areas are involved in the RHI.

1.3.5.6 Posterior Parietal Cortex and Rubber Hand Illusion

Given that evidence suggests that the processing of multisensory stimuli in peripersonal space, sensorimotor integration and RHI takes place in the parietal-frontal cortical
network, we will focus on PPC in this section. Peripersonal space is the immediate space surrounding our body (Holmes & Spence, 2004). In this space, visual information of external world is integrated with tactile information arising from own body, combining the mental representations of own body with stimuli from the external world (Brozzoli et al., 2012). Furthermore, the network involving PPC-premotor/motor areasis disrupted in patients with focal hand dystonia (Delnooz, Helmich, Toni, & van de Warrenburg, 2012; Pirio Richardson, Beck, Bliem, & Hallett, 2014; Vesia & Chen, 2014), supporting PPC-premotor involvement in RHI deficits.

Human fMRI studies have identified IPS, PMv, and the superior parietal occipital junction as a part of peripersonal space networks (Bremmer et al., 2001; Quinlan & Culham, 2007). The network codes visual stimuli presented in a space near a body part that receives tactile stimuli in a body-centered reference frame, allowing the integration of the external visual information around the body and the tactile information of a specific body part (Brozzoli et al., 2012). The bimodal neurons in the network responding to visual and tactile stimuli are modulated by the distance between the visual object and the tactile receptive field, with greater modulation in peripersonal space than in far space (Brozzoli et al., 2012). The close relationship between motor and sensory stimuli in peripersonal space implies that the peripersonal space also serves as a mediator for interactions between the sensory and motor systems.

In summary, several brain areas within the premotor-parietal network are involved in RHI. IPL is involved in proprioceptive shift but not in subjective RHI experience and body ownership. Because IPL is more related to visuo-motor integration rather than somatosensory-motor integration, other subdivisions in PPC such as SPL, which predominantly receives somatosensory inputs, may also be relevant to the RHI experience.

1.3.6 Multisensory Integration in PD patients
1.3.6.1 Multisensory Integration and its Involvement in Sensorimotor Integration in PD patients at the Behavioral Level

Multisensory integration and sensorimotor integration in PD patients have been tested at the behavioural level in several studies using different tasks. Visuo-auditory integration at the perceptual level was tested by a task in which facilitation of a motor response is normally found in healthy individuals. PD patients with freezing of gait show less of the visuo-auditory facilitation compared to age-matched HCs (Fearon et al., 2015), suggesting a deficiency of multisensory integration in PD patients. Haptic perception is another type of multisensory integration during which participants explore an object shape with the hands without vision, integrating tactile perception and proprioception. The haptic sensitivity is compromised in PD patients compared to similar age-matched HCs (Konczak, Li, Tuite, & Poizner, 2008; Konczak et al., 2012; Li, Pickett, Nestrasil, Tuite, & Konczak, 2010), suggesting impairment of tactile-proprioceptive integration. When the exploring movement was performed passively, it only involved tactile-proprioceptive multisensory integration without involving the motor system. However, when it was performed actively, sensorimotor integration occurred involving the motor system. Active haptic threshold increases in PD patients compared to HCs, suggesting the impairment of multisensory integration and sensorimotor integration (Konczak et al., 2008; Konczak et al., 2012).

It is not known whether the altered sensorimotor integration in PD patients was attributed to the stage where multisensory inputs are integrated or a later stage of sensorimotor integration. Elevated haptic thresholds in both active and passive explorations implies that PD affects an early stage of multisensory integration that eventually influences sensorimotor integration (Konczak et al., 2012). However, even in the passive exploration paradigm, separation of multisensory integration from kinetic feedback from moving arm is unavoidable, resulting in inability to distinguish a deficit in the process of multisensory integration from a deficit in sensorimotor integration. In this view, examining the extent of RHI may be useful to assess multisensory integration. Multisensory integration for body representation and peripersonal space has not been
investigated in PD patients. When compared to HCs, PD patients also have a tendency to rely more on external sensory inputs such as vestibular or visual information than internal representation of body during an orientation determination task (Barnett-Cowan et al., 2010). This suggests abnormal interaction between the external sensory inputs and the mental representations of own body.Erroneous mental rotation of hand (Amick, Schendan, Ganis, & Cronin-Golomb, 2006; Dominey, Decety, Broussolle, Chazot, & Jeannerod, 1995) and slow motor imagery (Helmich, de Lange, Bloem, & Toni, 2007) reported in PD patients may indicate an altered process of multisensory integration for body representation.

Determining how sensorimotor integration is modulated in PD patients will provide a better understanding of the underlying mechanisms in multisensory integration.

1.3.6.2 Posterior Parietal Dysfunction in PD patients

As described above, PPC plays a crucial role in multisensory integration and sensorimotor integration. The loss of dopaminergic projections from basal ganglia leads to abnormal cortical activation patterns in M1 and other cortical areas including PPC - probably due to aberrant control of the ascending thalamocortical system (Marsden & Obeso, 1994). Therefore, PPC likely contributes to the altered multisensory and sensorimotor integration leading to deficits at the behavioural level in PD patients.

The altered activation in PPC in PD has been reported in several neuroimaging studies. Fluorodeoxy glucose (FDG) PET studies have repeatedly shown reduced metabolic activities in parietal association cortex together with premotor and prefrontal cortex at rest (Lozza et al., 2004; Ma, Tang, Spetsieris, Dhawan, & Eidelberg, 2007; Moeller et al., 1999; Samuel et al., 1997). These studies utilized spatial covariant analysis and revealed that the reduced activities in these areas were associated with PD-related motor scores (Eidelberg, 2009; Ma et al., 2007). Resting state fMRI also reported reduced activity in PPC and prefrontal cortex in PD patients with freezing of gait (Tessitore et al., 2012). fMRI also shows that increased activity in superior parietal
cortex at rest in PD patients (Wu et al., 2015). During movements, inferior parietal cortex together with lateral premotor cortex is over activated in PD patients compared to HCs (Samuel et al., 1997). With motor tasks, the activation in PPC is abnormally increased in PD patients (Catalan, Ishii, Honda, Samii, & Hallett, 1999; Samuel et al., 1997; Tessa et al., 2010). Abnormal activation in PPC is also observed during motor imagery (Helmich et al., 2007). These imaging studies imply altered PPC activation in PD patients leading to abnormal sensorimotor integration.

A decreased functional connectivity between PPC and pre-supplementary motor area (pre-SMA), a motor related area, has been found at rest (Wu et al., 2011). Functional connection between PPC and M1 can also be studied using paired-pulse TMS paradigm with two coils. So far, only one TMS study investigated PPC-M1 interactions at rest in PD patients. In the study, PPC was defined as IPL. It revealed a lack of facilitatory interaction between PPC and M1 in PD patients (Palomar et al., 2013). The study supported the hypothesis that PPC may be involved in the altered sensorimotor integration in PD patients, suggesting a possible key role in multisensory integration deficits in PD patients.

However, PPC-M1 interactions in response to multisensory integration in PD patients has not been investigated.
2  RESEARCH AIMS and HYPOTHESIS

2.1 Objectives of the Present Thesis

2.1.1 Study One: Modulation of Sensorimotor Integration by Rubber Hand Illusion in Healthy Subjects

The primary purpose of this study is to establish the validity of a paradigm to assess how RHI-induced multisensory integration impacts on sensorimotor integration and the interactions between PPC and M1. The RHI was used to evoke and assess visuotactile-proprioceptive integration. In this study, healthy subjects were tested.

Behavioral studies have suggested that RHI altered somatosensory processing (Folegatti et al., 2009; G. Lorimer Moseley et al., 2008) and interfered with motor performance. However, the neurophysiological underpinnings for the modulation of somatosensory processing by the RHI remain unclear. The first specific aim of the Study One is to examine neurophysiology of RHI modulation of sensorimotor integration by measuring the extent of SAI and LAI (i.e. the MEP amplitude ratio) during RHI with TMS. The second specific purpose of the study is to investigate the modulation of the interaction between PPC and M1 during RHI using the paired-pulse TMS approach with two coils.

2.1.2 Study Two: Modulation of Sensorimotor Integration by Rubber Hand Illusion in Parkinson’s Disease Patients

The primary purpose of Study Two is to assess abnormalities in multisensory integration and its influence on sensorimotor integration in patients with PD by applying the methods established in Study One. The results from PD patients were compared with those from age-matched HCs (HC). In addition, the influence of dopaminergic
medications was investigated by comparing the results in the on and off medication states.

The firstly, whether PD patients have deficits in visuo-tactile-proprioceptive integration induced by RHI was evaluated at the behavioral level. The secondly, the modulations of SAI and LAI during RHI was measured. Thirdly, the influence of RHI on the PPC-M1 interaction was investigated.

2.2 Hypotheses of the Present Thesis

2.2.1 Study One: Modulation of Sensorimotor Integration by the Rubber Hand Illusion in Healthy Subjects

We hypothesize that the extent of SAI and LAI at baseline will decrease during RHI due to suppression of somatosensory processing. We also hypothesize that PPC-M1 interaction will be reduced during the RHI.

2.2.2 Study Two: Modulation of Sensorimotor Integration by the Rubber Hand Illusion in Parkinson’s Disease Patients

We hypothesize that PD patients will experience less RHI (i.e. weaker subjective RHI feeling and smaller proprioceptive arm shift) than age-matched HC at the behavioral level. The modulation of SAI and LAI by RHI will be reduced in PD patients compared to HC. The dopaminergic medications will normalize the modulation of SAI and LAI by RHI. The PPC-M1 interaction in PD patients will be less influenced by the RHI than HC. The modulation of the PPC-M1 interaction by the RHI will be normalized by the dopaminergic medications.
3 STUDY ONE: Modulation of Sensorimotor Integration by Rubber Hand Illusion in Healthy Subjects

3.1 Abstract

The rubber hand illusion (RHI) paradigm experimentally manipulates multisensory integration involving visual, tactile and proprioceptive inputs by simultaneously stroking a rubber hand in view and a participant’s visually occluded hand, and produces an illusion of rubber hand ownership and arm shift. The posterior parietal cortex (PPC) is an important area for multisensory integration. Although motor control requires multisensory inputs to be transformed into motor outputs, whether the RHI modifies the interactions between sensory and motor systems remains unclear. We examined the functional connections from the primary sensory and association cortices, and from the PPC to the primary motor cortex (M1) during the RHI. In Experiment 1, short-latency afferent inhibition (SAI) and long-latency afferent inhibition (LAI) were measured using transcranial magnetic stimulation (TMS) before and immediately after a synchronous (RHI) or an asynchronous (control) condition. In Experiment 2, PPC-M1 interaction was measured using paired-pulse TMS with two coils. We found that SAI and LAI were reduced in the synchronous condition compared to baseline, suggesting that the RHI decreased the functional connections from the primary sensory and the association cortices to M1. We also found that greater inhibitory PPC-M1 interaction was associated with stronger RHI assessed by questionnaire. Our findings suggest that the RHI modulates sensorimotor integration at the early and late stages by reducing the gain of tactile processing to resolve conflicts among multisensory inputs.

Keywords: Rubber hand illusion, transcranial magnetic stimulation, short- and long-latency afferent inhibition, multisensory integration, posterior parietal cortex
3.2 Introduction

The status of our body is perceived and mapped in broad brain networks. Somatosensory information such as tactile, proprioceptive, and visual inputs regarding one's own body parts first arrives at the primary sensory area and are then integrated in the association areas including the posterior parietal cortex (PPC), the ventral premotor cortex (PMv) and the temporo-parietal junction (TPJ) (G. L. Moseley et al., 2008; Serino et al., 2013). Because lesions of these areas can lead to decreased awareness of the ownership or location of one's own body part (Giummarra, Gibson, Georgiou-Karistianis, & Bradshaw, 2008), integration of multisensory inputs seems to be essential for perceiving our body ownership and location.

Multisensory integration for body perception can be experimentally manipulated by a paradigm known as "rubber hand illusion (RHI)" (Botvinick & Cohen, 1998). A participant observes a rubber hand in view being stroked with a paintbrush while his or her visually occluded own real hand is being stroked simultaneously with another paintbrush. When the touches of the two brushes are synchronized, the participant often experiences an ownership feeling over the rubber hand and perceives a shift of own hand's position towards the rubber hand. These illusory experiences are thought to occur as a result of an integration of synchronized visual capture of the rubber hand being touched and tactile inputs from the occluded own hand (Botvinick & Cohen, 1998; Makin et al., 2008). Unlike natural circumstances, multisensory integration evoked by the RHI paradigm creates a conflict between vision and tactile inputs. The conflict is thought to be resolved by modulating the sensory inputs gain: increasing the gain of reliable visual inputs, and decreasing the gain of incongruent somatosensory inputs (Dempsey-Jones & Kritikos, 2014; Makin et al., 2008). Reduction of somatosensory inputs from own hand, especially tactile processing, has been suggested by behavioural studies (Folegatti et al., 2009; G. L. Moseley et al., 2008; Zopf et al., 2011).

Skilled motor behaviours rely on the integration of motor commands with sensory information from various modalities, a process termed sensorimotor integration. Therefore, changing the gain of multisensory integration may influence the motor
However, the influence of the RHI on the motor system has shown inconsistent results in behavioural studies (T. Heed et al., 2011; Kammers, de Vignemont, et al., 2009; Kammers, Verhagen, et al., 2009). Decreased motor performance with “affected” own hand after the RHI was demonstrated in a study (T. Heed et al., 2011) while other studies showed no impact of the RHI (Kammers, de Vignemont, et al., 2009; Kammers, Verhagen, et al., 2009). Recent work shows a decrease in corticospinal excitability associated with own hand disembodiment during the RHI (Della Gatta et al., 2016). However, the neurophysiological basis of altered tactile somatosensory processing during RHI and its influence on sensorimotor integration has not been investigated.

The PPC, a multimodal sensory integration area, receives abundant inputs from sensory cortices and has strong projections to M1 and other motor areas (Petrides & Pandya, 1984). It is a critical node for transforming multimodal sensory inputs into motor commands. In addition, a study showed a modulation of tactile sensitivity through the PPC when there was a conflict between visual and tactile inputs (Ro, Wallace, Hagedorn, Farnè, & Pienkos, 2004). Therefore, the PPC may play a role in modulations of sensory gain during the RHI.

In the present study, we used transcranial magnetic stimulation (TMS) to assess how the RHI modulates the influence of tactile somatosensory input on M1 excitability. We examined short-latency afferent inhibition (SAI), which reflects direct impact of the primary somatosensory cortex (S1) on M1, and long-latency afferent inhibition (LAI), which likely represents the influence of secondary sensory and association areas including multisensory areas such as the PPC or the premotor cortex on M1 (Sailer et al., 2003). We also investigated functional connectivity from PPC to M1 immediately after the RHI. We hypothesized that SAI and LAI would be reduced immediately after the RHI due to reduced somatosensory influences from gating mechanisms and that PPC-M1 interaction would be weakened as a result of reduced reliance on somatosensory inputs after the RHI.

### 3.3 Methods
3.3.1 Subjects

Thirty-one healthy volunteers (15 women, age 43.3 ± 18.9 years, mean ± SD; range, 21-77 years) participated in the study. All but one were assessed as right handed by the Edinburgh Handedness Inventory (Oldfield, 1971). All participants gave written informed consent. University Health Network Research Ethics Board approved the protocol. We tested twenty-seven subjects (12 women; age 44.7 ± 18.9 years) in Experiment 1 and twenty-six subjects (13 women; age 45.2 ± 19.0 years; 22 subjects from Experiment 1) in Experiment 2. All the participants gave written informed consents and the protocol was approved by University Health Network Research Ethics Board.

3.3.2 Rubber Hand Illusion (RHI) and behavioural assessments

We used the RHI task originally reported by Botvinick and Cohen (Botvinick & Cohen, 1998) in the current study. Our experimental set-up is illustrated in Figure 6A. A life-sized rubber right hand was presented in an anatomically congruent way on a table, and the participant’s own real right hand was placed lateral to the rubber hand (15 cm from the real hand). Prior to the induction of the RHI, a movable black board covered both hands with a measurement tape. Participants estimated the position of their right hidden index finger by naming the corresponding number on the measurement tape (Proprioceptive Judgment: PJ). The judgment was repeated six times with the onset and offset numbers on the tape being changed for each judgment to avoid biases. The distance between the actual and the estimated finger positions was averaged and used as estimated hand position at baseline. Then, the movable black board was replaced by a black partition set between the rubber hand and the participants’ hand to occlude only the own hand’s view for the RHI induction. The dorsal surface of index fingers of both the rubber and the own hands were touched by an experimenter using two paintbrushes with brisk strokes at approximately 1 Hz for three minutes (about 180 brush strokes in total) while participants attended to the rubber hand. We tested two conditions, synchronous and asynchronous conditions. In synchronous condition, the two brushes were moved synchronously in terms of timing while in asynchronous condition, the timing between the two brushes was delayed with approximately 500 ms. The PJ was repeated.
immediately after the RHI induction. At the end of each condition, a questionnaire consisted of 9 statements (Botvinick & Cohen, 1998) was administered to quantify the subjective feeling of embodiment of the rubber hand. The first three statements (Q1-3) concern the RHI experiences (1. I felt as if the rubber hand were my own hand, 2. It seemed as if I were feeling the touch of the paintbrush in the location where I saw the rubber hand touched, 3. The touching of the rubber hand felt just like an actual touch) and the other 6 statements were controls (Botvinick & Cohen, 1998). Participants rated their agreement to each statement by marking on a 14 cm-long visual-analog scale (0=completely disagree, 14=completely agree).

3.3.3 Digital nerve stimulation (DNS)

Electrical stimulation was applied to the palm side of the right index finger over the distal and middle phalanx through small pad electrodes (size, 28mm x 20 mm) with cathode positioned proximally using a DS7A constant-current stimulator (pulse width 0.2ms; Digitimer, Welwyn Garden City, UK). Sensory threshold (ST) was determined as the lowest intensity felt in three consecutive trials by the participants and the stimulus intensity was set at 3ST for SAI and LAI (Chen, Corwell, & Hallett, 1999; Sailer et al., 2003).

3.3.4 Surface electromyography (EMG) recording

Surface electromyography (EMG) was recorded from the relaxed right first dorsal interosseous (FDI) muscle using Ag-AgCl electrodes with the active electrode on the muscle belly and the reference electrode over the right metacarpophalangeal joint. The EMG signals were amplified (1000 X), filtered (band pass 20 Hz-2.5kHz; Intronix Technologies Corporation Model 2024F, Bolton, Ontario, Canada), digitized at 5kHz by an analog-to-digital (A/D) interface (Micro 1401, Cambridge Electronics Design,
Cambridge, UK) and stored in a laboratory computer for off-line analysis using SIGNAL software (Cambridge Electronic Devices, Cambridge, UK).

3.3.5 Transcranial magnetic stimulation (TMS)

Transcranial magnetic stimulation (TMS) was performed using a Magstim2002 stimulator (Magstim, Whitland, UK) and a custom figure-of-eight coil (diameter, 50 mm). The area for eliciting the best motor response in the right FDI muscle was established over the left M1 with posterior to anterior induced current direction, and the coil position was marked on the scalp as the motor hot spot. The test stimulus (TS) intensity was adjusted to evoke ~ 1 mV peak-to-peak motor evoked potential (MEP) amplitude from the relaxed right FDI muscle. Peak-to-peak MEP amplitude for each trial was measured and averaged for each stimulation conditions.

3.3.5.1 Experiment 1: Influence of the RHI on SAI and LAI

In Experiment 1, we measured SAI and LAI reflecting sensorimotor integration. The maximum inhibitory effects of MNS at the wrist on M1 occur with inter-stimulus intervals (ISIs) at around 20 ms (Tokimura et al., 2000) and 200 ms (Chen et al., 1999). To account for the peripheral sensory conduction time from the digit to the wrist, 3 ms was added for DNS (Chen et al., 1999; Sailer et al., 2003). Each run consisted of 3 different conditions: test stimulus (TS) alone, DNS followed by TS at ISI of 23 ms for SAI (DNS$_{23}$-TS), and at ISI of 203 ms for LAI (DNS$_{203}$-TS). These conditions were delivered in a random order and repeated 11 times 5s apart.

3.3.5.2 Experiment 2: The influence of the RHI on the interaction between the posterior parietal cortex (PPC) and the primary motor cortex (M1)
The left PPC-M1 interaction was assessed with a paired-pulse TMS paradigm with two coils (Karabanov et al., 2014; Koch et al., 2007; Rothwell, 2011; Vesia et al., 2013). TS intensity was adjusted to evoke ~ 1 mV MEP amplitudes. Each run consisted of 5 conditions with different ISIs (TS alone; CS followed by TS, CS-TS at 4, 6, 8, or 10 ms of ISI) delivered in random order and repeated 9 times each. Inter-trial interval was 5s.

To identify the left PPC, we acquired T1-weighted magnetic resonance images (MRI) from 19 participants using a 3.0 T MR scanner (General Electric; 500µ in-plane resolution; gradient-echo spiral EPI sequences) before the study visit. A frameless stereotaxic neuronavigation system (Brainsight2 Rogue Research, Canada) was used. We localized the left medial and anterior part of superior parietal lobe (SPL), a subregion within the PPC, according to individually identified anatomical landmarks. SPL was defined by a region medial to the intraparietal sulcus, posterior to the postcentral sulcus, and anterior to the parieto-occipital sulcus (Figure 7). The mean Talairach coordinates were x=19.9±5.5, y=-73.2±11.1, z=61.7±10.4. The mean Euclidean distance between the two coils was 6.9 ± 1.5 cm. For seven participants who did not undergo the MRI due to various reasons (e.g. metals in the body, limited time commitment or personal preference), CP1 in the International 10-20 electroencephalogram (EEG) electrode system was used to locate the left SPL (Koessler et al., 2009). The mean Euclidean distances between the two coils were comparable with 6.9 ± 1.8 cm for the seven subjects and 6.7 ± 1.3 cm for the other nineteen subjects.

A conditioning stimulus (CS) was delivered with a custom 40mm figure-of-eight coil placed over the left PPC in a posterior-anterior current (Ziluk et al., 2010). The TS coil was placed over the left M1 at the optimal position for the right FDI muscle. Figure 1D illustrates the coil positions. The CS intensity was set at 90% of resting motor threshold (RMT), which was determined from the motor hot spot as the lowest intensity that evoked more than 50µV peak-to-peak amplitude MEPs in 5 out of 10 consecutive trials (Rossini et al., 2015).
3.3.6 Experimental Designs

We tested the influence of the RHI on SAI and LAI in Experiment 1, and the effects of the RHI on PPC-M1 interaction in Experiment 2 on separate days. The study design is illustrated in Figure 6B. Each experiment started with baseline TMS measurement followed by proprioceptive judgment. After the RHI induction either with the synchronous or asynchronous condition, the proprioceptive judgment and the TMS measurements were repeated. The participants kept their right hand still until the completion of the TMS measurements. After the questionnaire, the participants were given a five-minute break, during which they moved the right hand to cancel the RHI effect. Then, the other condition was tested with the same procedure. The order of the synchronous and asynchronous conditions was randomized and counterbalanced across subjects.
A) **Experimental set-up for rubber hand illusion (RHI) paradigm.** The participants were seated with their right arm rested at a table and their left arm rested on their laps. A rubber right hand was placed in an anatomically congruent way on the table, 7 cm to the right of the midline of the participant. The participant’s actual right hand was positioned 15 cm lateral to the rubber hand. A black cloth was used to cover the participants’ right shoulder, elbow and arm as well as the proximal parts of the rubber hand. An experimenter simultaneously touched the participant’s hand and the rubber hand with two paintbrushes with synchronous (RHI condition) or asynchronous (control condition) strokes while the participant attended to the rubber hand for three minutes.

B) **Study design.** TMS Baseline: The experiment started with baseline measurements of TMS parameters, which were SAI and LAI in Experiment 1 and
the PPC-M1 interaction in Experiment 2. Proprioceptive judgement (PJ) baseline: PJ at baseline was assessed immediately before the induction of the RHI. RHI sync: induction of RHI using synchronous brush strokes. RHI async: induction period using asynchronous brush strokes. PJ post: PJ was assessed immediately after the RHI induction in each condition. TMS post sync/async: the TMS measurements were repeated immediately after the PJ post with the participant’s hand stayed still. Questionnaire (Q): after completing the TMS post measurement in each condition, the participants filled out the questionnaire. The order of the synchronous and asynchronous conditions was randomized.
Figure 7 Stimulation of PPC with TMS

Figure 7. **Left:** Location of the left PPC target in a representative participant. The left SPL (superior parietal lobe) was identified in 3D reconstruction of the brain as the medial and anterior part of the superior parietal lobe, medial to the intraparietal sulcus, anterior to the parieto-occipital sulcus, and posterior to post-central gyrus. (Mean Talairach coordinates ± SD: x -19.9±5.5, y 73.2±11.1, z 61.7±10.4). **Right:** Schematic view of the paired-pulse TMS with two coils to examine the PPC (posterior parietal cortex) - M1 (primary motor cortex) interaction. In order to probe the influence of PPC on M1, conditioning stimuli (CS: 90% RMT) were applied to the PPC before test stimulus (TS) were delivered to M1.
3.4 Data Analysis

To avoid learning experience of the RHI at the behavioural level, the behavioural data from the first visit was used in 22 participants who participated in both Experiments 1 and 2, except for a correlation analysis in Experiment 2. In Experiment 2, the RHI scores obtained from the same visit was used to examine the relationship between the behavioural result and the neurophysiological change (see correlation analysis below). All the analyses were conducted with SPSS 17.0 and significance was set at P < 0.05 unless otherwise stated.

The questionnaire rating scores for the first three statements (Q1-3) concerning the RHI experiences and the other six control statements were averaged separately for the synchronous or asynchronous condition. Based on well-established results of the RHI questionnaire in previous studies (Botvinick & Cohen, 1998; Longo, Schüür, Kammers, Tsakiris, & Haggard, 2008; Tsakiris & Haggard, 2005), we predicted that the average scores for Q1-3 would be larger than the control statements in the synchronous condition. To compare the scores for Q1-3 with the control statements in the synchronous condition, a paired one-tail t-test was used. Similarly, we also predicted that the scores for Q1-3 in the synchronous condition would be larger than the scores for the asynchronous condition. We used a separate paired one-tail t-test to compare the average scores for Q1-3 in the synchronous and the asynchronous conditions.

The estimated hand positions in proprioceptive judgment were analyzed in the similar way. As we predicted that the hand position in the synchronous condition would be significantly larger than the asynchronous condition based on previously established results (Botvinick & Cohen, 1998; Longo et al., 2008; Tsakiris & Haggard, 2005), we used a paired one-tail t-test to compare the hand position in the synchronous with the one in the asynchronous condition. Baseline hand position in these two conditions was separately compared using another paired one-tail t-test to confirm no significant differences at baseline.
In Experiment 1, SAI and LAI were expressed as a ratio of the conditioned (DNS23-TS, DNS203-TS) to the unconditioned (TS alone) MEP amplitudes. We defined that there is no SAI or LAI at baseline if the MEP ratio exceeds 1.0 (Sailer et al., 2003). Participants without SAI or LAI at baseline were excluded from the analysis because our aim was to investigate the effects of the RHI on SAI and LAI. Both SAI and LAI were normally distributed as determined by Kolmogorov-Smirnov normality tests. The effects of the RHI on SAI or LAI were assessed using repeated measures ANOVA with the factor CONDITION (baseline, synchronous, asynchronous) as the repeated measure.

In Experiment 2, the MEP amplitudes at each ISI were expressed as a ratio of the conditioned (CS-TS at ISI 4, 6, 8, and 10 ms of ISIs) to the unconditioned (TS alone) MEP amplitudes. Ratios <1 indicate inhibitory and ratios>1 indicate facilitatory influences of CS to M1. The effect of different ISIs on PPC-M1 interaction at baseline was first compared using one-way repeated measures ANOVA with ISIs (4, 6, 8, and 10 ms) as the repeated measures. Then, the influence of the RHI on PPC-M1 interaction was analyzed using two-way repeated measures ANOVA with CONDITION (baseline, synchronous, asynchronous) and ISIs (4, 6, 8, and 10 ms) as repeated measures. Significant effects were further analyzed by paired-t test with Bonferroni correction for multiple comparisons. In addition, correlation between the strength of the RHI and modulation of the PPC-M1 interaction was analyzed. The MEP ratios were averaged across different ISIs in each individual because there were no significant differences between ISIs. The correlation between the average Q1-3 scores in Experiment 2, and the average MEP amplitude was analyzed using Pearson correlation for the synchronous or asynchronous condition separately.

3.5 Results

3.5.1 Questionnaire on the Rubber Hand Illusion Experiences
The scores of agreements to statements 1-3 (Q1-3: the RHI related experiences) and the six control statements are shown in Figure 7A. We found higher agreement for Q1-3 in the synchronous condition compared to the asynchronous condition [paired t-test, $t(30)=8.87$, $p<0.001$]. We also confirmed that the Q1-3 was scored higher than the control statement in the synchronous condition [paired t-test, $t(30)=9.55$, $p<0.001$].

### 3.5.2 Proprioceptive judgment (PJ)

The estimated index finger positions at baseline and post RHI induction are shown in Figure 7B. Participants perceived their hand drifted more towards the position of the rubber hand after the synchronous compared to the asynchronous stimulation [$t(30)=1.81$, $p=0.04$]. At baseline, no significant difference in their perceived hand positions was detected between the synchronous and the asynchronous conditions [$t(30)=0.80$, $p=0.22$].
Figure 8 Behavioural Results

A) Questionnaire results. The mean rating scores for the RHI experience statements (Q1-3) and for the control statements (Control) in the synchronous (RHI) and the asynchronous (control) conditions (maximum score = 14). The score for Q1-3 in the synchronous condition was significantly higher than that in the asynchronous condition (p<0.001, n=31). Q1-3 was scored significantly higher than the control statements. Error bars denote the standard error of the mean (SEM).

B) Proprioceptive judgments before (baseline) and immediately after (post) the brush strokes in the
synchronous and the asynchronous conditions. The Y-axis denotes the distance from the position of own real hand toward the rubber hand with the own hand position at 0 cm. Participants perceived their hand shifted more towards the rubber hand in the synchronous stimulation than the asynchronous stimulation \[t(30)=1.81, p=0.04\]. Error bars indicate the standard error of the mean (SEM).
3.5.3 Experiment 1: Modulation of Short- and Long-latency Afferent Inhibition by RHI

Five participants did not show SAI at baseline (MEP ratio >1.0) and were excluded from the analysis for SAI. Therefore, 22 participants (age 43.5±19.2 years) were included in the analysis. The findings are shown in Figure 8A. SAI in the synchronous condition was significantly reduced compared to the baseline (p=0.042). Repeated measures ANOVA revealed a significant main effect of CONDITION \[F(2,20)=4.31, p=0.028\]. Post-hoc comparison showed that SAI in the asynchronous condition was not significantly different from that of the baseline or the synchronous condition.

Figure 8B shows the result for LAI. Four participants who did not show LAI at baseline (MEP ratio >1.0) were excluded from the analysis. Therefore, 23 participants (age 41.2±18.1 years) were included in the analysis. We found a significant reduction in LAI after the synchronous condition compared to the baseline (p=0.047). Repeated measures ANOVA showed a significant effect of CONDITION \[F(2,21)=5.31, p=0.014\] for LAI. Post hoc analysis revealed that LAI after the asynchronous condition did not differ significantly from the baseline or the synchronous condition.
A) **The effect of RHI on Short-latency afferent inhibition (SAI).** SAI at baseline (in black), and after the synchronous (RHI, in light grey) and asynchronous (control, in darker grey) conditions were shown in three bar graphs. Y-axis denotes the MEP amplitudes, which are expressed as ratios to the mean MEP of the unconditioned (TS alone) trials. Values below 1 indicate inhibition. SAI at baseline was significantly reduced in the synchronous condition (p=0.042) but not in the asynchronous condition (p=0.23) compared to the baseline. Error bars denote the standard errors of the mean (SEM).

B) **The effect of RHI on Long-latency afferent inhibition (LAI).** LAI at baseline,
synchronous (RHI), and asynchronous (control) conditions. LAI at baseline was reduced in the synchronous condition compared to the baseline (p=0.049). The LAI was not modified in the asynchronous condition (p=0.19). Error bars denote SEM.
3.5.4 Experiment 2: Modulation of the PPC-M1 interaction by the RHI

Figure 9A shows the result for the PPC-M1 interaction (n=26). At baseline, one-way repeated measures ANOVA showed no effect of ISI, confirming the results of a previous study (Ziluk et al., 2010). Modulation of the PPC-M1 interaction by the RHI was assessed by two-way repeated measures ANOVA, which revealed no overall main effect of CONDITION [F(2,24)=0.67, p=0.52], ISI [F(3,23)=1.17, p=0.34] or interaction between CONDITION and ISI [F(6, 20)=1.13, p=0.38].

We investigated whether the PPC-M1 interaction after the RHI induction correlated with the strength of the RHI. Figure 9B illustrates the relationship between the average score for Q1-3 in the rubber hand ownership questionnaire and the averaged PPC-M1 interaction across different ISIs in the synchronous condition. Pearson correlation revealed that stronger rubber hand ownership was correlated with greater inhibitory PPC-M1 interaction in the synchronous condition (r2=0.212; p=0.018). The strength of the rubber hand ownership did not correlate with the PPC-M1 interaction in the asynchronous condition (Figure 9C).
A) The functional connection from PPC to M1 at baseline, after synchronous (RHI) or asynchronous (control) brush strokes. Group-averaged ±standard error of the mean (SEM) (n=26) with MEP amplitudes expressed as ratios to the
unconditioned MEP for each ISI are shown. There were no significant differences across the three conditions.

B) and C) **Relationship between the RHI strength and the PPC-M1 interaction in the synchronous (B) and asynchronous (C) conditions.** The RHI strength assessed by questionnaire (Q1-3) significantly correlated with the greater inhibitory PPC-M1 interaction only in synchronous condition ($r^2=0.212; p=0.018$) but not in asynchronous condition ($r^2=0.002; p=0.812$).
3.6 Discussion

We found that the RHI reduced SAI and LAI, suggesting the involvement of S1 and the sensory association areas, most likely the multisensory integration areas in the RHI induction. We also displayed that the stronger ownership of the rubber hand was associated with greater inhibitory influence of PPC over M1. These findings show that modulating the sense of ownership over one’s hand is capable of altering both the early and later processing of tactile afferent, as well as their integration at the level of their motor outputs.

3.6.1 Behavioural results confirmed the synchronous condition induces RHI

In agreement with previous work (Botvinick & Cohen, 1998; Ehrsson, Spence, & Passingham, 2004; Longo et al., 2008; Tsakiris & Haggard, 2005), our RHI behavioural results confirmed that the synchronous but not the asynchronous condition induces specific changes. The three statements on the RHI questionnaire (Q1-3) assess cognitive changes in body ownership and body awareness regarding the RHI (Botvinick & Cohen, 1998; Ehrsson et al., 2004; Longo et al., 2008; Tsakiris & Haggard, 2005). It has been suggested that the ownership feeling is induced as a result of visuo-tactile-propiroceptive multisensory integration (Botvinick & Cohen, 1998; Makin et al., 2008; Tsakiris & Haggard, 2005). In turn, the established ownership feeling influences the multisensory integration by gating sensory inputs coming from own hand, specifically reducing the weight of incongruent inputs (Tsakiris, 2010).

3.6.2 The RHI Reduces Short-lateness Sensorimotor Integration

SAI measures short-latency sensorimotor integration and likely reflects a direct projection from S1 to M1 (Chen et al., 1999; Tokimura et al., 2000). We found that SAI
was reduced in the presence of the RHI. The reduction of SAI in the synchronous condition may thus be taken to indicate the reduced connection between S1 and M1 during the RHI. Interestingly, increased SAI was reported while observing brush stroking of another person’s hand (Wood, Gallese, & Cattaneo, 2010). However, the gating mechanism could occur at S1, thalamus or the spinal cord. Reduced SAI with the RHI may also reflect a gain change in the tactile inputs into S1, resulting in reduced processing of the tactile signals. Indeed, S1 involvement during the RHI has been suggested in other neurophysiological studies (Aspell, Palluel, & Blanke, 2012; Shokur et al., 2013). Body swap illusion which involves an illusory ownership and perceived shift of a whole body instead of a hand corresponding to the RHI, lead to an enhanced early component (P40) of tibial nerve somatosensory evoked potentials (SEP) which presumably correspond to N20 of median nerve SEP (Aspell et al., 2012). The reduced tactile somatosensory processing in S1 during the RHI may explain delayed tactile perception after the RHI (Folegatti et al., 2009).

Noteworthy, baseline SAI level in our study was lower compared to previous studies which used MNS at the wrist (Chen et al., 1999; Sailer et al., 2003; Tokimura et al., 2000). The lower SAI level at baseline can be explained by the fact that we used DNS to avoid contraction of thenar muscles which may disrupt the RHI. However, most of our participants demonstrated the MEP ratio < 1.0 at baseline, which suggests an inhibitory influence of DNS on M1 at short-latency in line with previous studies using DNS (Chen et al., 1999; Sailer et al., 2003).

3.6.3 The RHI Reduces Long-latency Sensorimotor Integration

Reduction of LAI with

We found LAI at baseline in most participants, in line with previous literature. We found that the RHI also reduced LAI and think that the reduction of LAI may reflect multisensory integration. Although anatomical correlates of LAI are not entirely understood, LAI has been suggested to involve association areas such as the
secondary sensory area, the PPC, the premotor cortex, and the basal ganglia (Chen et al., 1999; Sailer et al., 2003), linking sensory systems with motor systems. Some of these areas, the PPC and the premotor cortex, in particular, have shown to respond to multisensory inputs (Andersen, 1997; Rizzolatti, Fogassi, & Gallese, 1997) serving as multisensory integration areas. Several functional imaging studies have reported the involvement of multisensory processing areas including the PPC, the premotor cortex, the intra-parietal sulcus, the lateral occipito-temporal cortex, and the putamen in the RHI (Ehrsson, Holmes, & Passingham, 2005; Ehrsson et al., 2004; Limanowski & Blankenburg, 2015a, 2015b). In addition, the RHI led to attenuation of SEPs in the frontal and parietal areas at latencies of ~50 ms, (Zeller, Litvak, Friston, & Classen, 2015) and enhancement of SEPs in the sensorimotor areas at longer latencies (140 - 460 ms) (Aspell et al., 2012; Peled, Pressman, Geva, & Modai, 2003; Press, Heyes, Haggard, & Eimer, 2008). These studies indicate that multisensory integration cortices in the fronto-parietal association areas are involved in the RHI. These results may not be directly comparable to ours because most of them assessed the RHI changes during the RHI induction with hand stroking while our assessments were performed immediately after the RHI induction. However, we conducted TMS assessments while the RHI was still present. Therefore, the reduced LAI reported here likely reflects the modulation of the multisensory integration cortices by the RHI. It may also imply increased errors in the motor performance of the affected hand after the RHI (Heed et al., 2011) because motor planning requires proper multisensory integration in the PPC.

Of note is that baseline LAI in our study was lower than several previous studies that used MNS, for the similar reason with SAI at baseline although most participants in our study showed LAI at baseline in line with previous literature (Chen et al., 1999; Sailer et al., 2003).

Reduced LAI with the RHI may be explained by reduced tactile gain in the multisensory association cortices, similar to SAI reduction. The reduced gain of somatosensory processing during the RHI could be due to a conflict between visual, tactile and proprioceptive inputs. Ownership of a body part is thought to arise from the cognitive processes of judging congruencies of the body part in view with body images pre-stored
in the brain and built upon multisensory integration (Tsakiris, 2010). During the RHI induction, the tactile perception of brush strokes in one’s hand is temporally congruent with the visual capture of the rubber hand being touched, but is not spatially congruent with the proprioceptive information from one’s own hand. The congruent visual and tactile inputs are integrated and evoke an illusory ownership of the rubber hand, which then reinforces the dominance of the visual information over the conflicting proprioceptive signal and modifies the pre-stored body image (Makin et al., 2008; Ro et al., 2004). As a result, the gain for proprioceptive and tactile inputs may be reduced in S1 and association cortices for multisensory integration.

3.6.4 Inhibitory PPC-M1 interaction is associated with the strength of RHI

We displayed that greater inhibitory PPC-M1 interaction was associated with the strength of the RHI. Because the correlation between the greater inhibitory PPC-M1 interaction with the strength of the RHI was found only in the synchronous but not in the asynchronous condition, it likely represents a RHI-specific effect. Functional MRI studies have shown activation of the PPC during RHI (Ehrsson et al., 2005; Ehrsson et al., 2004; Gentile, Petkova, & Ehrsson, 2011). However, the PPC-M1 functional connection has not been examined during the RHI. A recent study demonstrated that M1 excitability was decreased during the RHI (Della Gatta et al., 2016; Miller & Farnè, 2016). Our finding supports this result; that is, the inhibitory influence from PPC to M1 may contribute to the decreased corticospinal excitability during the RHI.

The PPC is a multisensory integration area with abundant projections to the motor areas (Koch et al., 2007; Petrides & Pandya, 1984), and is involved in motor planning (Koch et al., 2008; Vesia & Crawford, 2012). The SPL within the PPC was chosen as the target. The SPL codes the location of the arm relative to other body parts (Andersen, 1997; Gentile et al., 2011; Lewis et al., 2011) and transforms multisensory inputs into a common coordinate system by visual, auditory and proprioceptive integration.
(Andersen, 1995; Lewis et al., 2011). This area is known to send intra-hemispheric inputs to the arm and hand representations in the M1 in human (Andersen, 1995; Andersen & Buneo, 2002; Premji, Rai, & Nelson, 2011; Ziluk et al., 2010). The SPL-M1 interaction was reported to be facilitatory at 6 ms ISI during vibratory tactile stimulation to the index finger while there was no facilitation or inhibition without stimulation (Ziluk et al., 2010).

In our study, the stronger the RHI was experienced, the more greatly reduced the somatosensory tactile processing was, leading to less facilitatory or even inhibitory PPC-M1 interactions. The PPC may play a role in reducing the somatosensory tactile gain during the RHI. A study reported a modulation of somatosensory tactile sensitivity under another type of visuo-somatosensory conflict. Transient suppression of the PPC by repetitive TMS showed a lack of the tactile sensitivity modulation, suggesting that the somatosensory gain may be altered through the PPC (Ro et al., 2004). The PPC also may be involved in resolving the visuo-somatosensory conflict evoked by RHI. Future studies may target other multisensory integration areas, such as the temporo-parietal junction and the ventral premotor areas during the RHI to describe their involvement in the maintenance of a stable sense of body ownership.

### 3.6.5 Clinical Implications of the findings

Abnormal RHI has been observed in some neurological and psychiatric disorders such as dystonia, schizophrenia, and autism (Fiorio et al., 2011; Paton, Hohwy, & Enticott, 2012; Peled et al., 2003). Focal hand dystonia, a disorder characterized by sustained or intermittent muscles contraction causing abnormal posture or repetitive movements, showed disrupted proprioceptive arm shift in the RHI indicating a failure in visuo-tactile-proprioceptive integration (Avanzino & Fiorio, 2014; Fiorio et al., 2011). Our findings support the hypothesis that dystonia is associated with abnormalities in multisensory integration areas (Delnooz, Helmich, Toni, & van de Warrenburg, 2012; Pirio

3.7 Conclusions

The RHI modulates sensorimotor integration by reducing the inhibitory influence of somatosensory input to M1. Thus, the effects of the RHI are not limited to the sensory areas but also encompass motor areas. The association between the greater inhibitory PPC-M1 interaction and the strength of the RHI suggests that the RHI involves modulation of the PPC-M1 interaction. Our findings imply that the RHI modifies sensorimotor integration pathway at multiple levels.

3.8 Acknowledgements

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4 STUDY TWO: Modulation of Sensorimotor Integration by Rubber Hand Illusion in Parkinson’s Disease

4.1 Abstract

Although motor features are considered the classical symptoms of Parkinson’s disease (PD), there are abnormalities in the sensory system. Sensorimotor integration, the neural process of transforming sensory inputs to motor outputs, is known to be altered in PD. However, the mechanism of the altered sensorimotor integration remains unclear. As sensorimotor integration is a part of a process of combining sensory inputs from different modalities known as multisensory integration, PD patients may have abnormality in multisensory processing affecting sensorimotor integration.

In the current study, we used RHI paradigm to evoke and assess visuo-tactile-proprioceptive integration. We examined and compared the level of RHI in PD patients and age-matched HCs. We also measured SAI, LAI, and functional connectivity between the posterior parietal cortex (PPC) and the primary motor cortex (M1) before and immediately after the RHI in each group. We found that PD patients experienced the RHI to the similar extent with the age-matched HCs, suggesting normal visuo-tactile-proprioceptive integration in PD patients regardless of dopaminergic medication states. Our result also revealed that, in PD-ON state, LAI during RHI was abnormally increased by dopaminergic medications while it was decreased in HCs. The negative correlation between the level of RHI and the inhibitory PPC-M1 interactions seen in HCs was lost in PD patients. Our results suggest that sensorimotor integration pathway which normally evoked by RHI is disrupted in PD patients and that sensorimotor integration is altered at multiple levels in PD.
4.2 Introduction

Parkinson’s disease (PD) is a progressive neurodegenerative disorder and is currently diagnosed largely based on its motor features. Disruption in the basal ganglia-motor cortex circuits is considered to account for the motor deficits. However, non-motor symptoms, including sensory problems, are common in patients with PD (S. Fahn et al., 2011) and it has been suggested that sensory abnormalities may contribute to motor deficits.

Sensory features in PD encompass pain, tingling or numbness of the affected limbs, and abnormal sensory processing such as decreased tactile processing and proprioceptive deficits. Because previous studies have consistently reported deficits in sensorimotor integration in PD patients, the abnormal sensory processing in PD patients may influence their motor performance by affecting sensorimotor integration. Behavioral studies demonstrated a failure of proprioceptive-motor integration in PD patients (Flash et al., 1992; Jobst et al., 1997; Rickards & Cody, 1997). TMS studies in PD patients also revealed abnormal sensorimotor integration. PD patients showed reduced LAI with off medication which was normalized by STN-DBS but not by dopaminergic medications. Although SAI was normal with off medication, dopaminergic medication reduced SAI (Sailer et al., 2003). SAI is likely to represent direct interaction between S1 and M1, while LAI possibly involves cortical association areas and the basal ganglia (Sailer et al., 2003). Therefore, S1, M1 and cortical association areas are likely involved in the altered sensorimotor integration in PD. However, the detailed cortical mechanisms involved in the impaired sensorimotor integration in PD has not been studied.

Multisensory integration, a process of converging sensory inputs from different sensory modalities, links closely with sensorimotor integration. Multisensory areas in the brain include the PPC and ventral premotor cortex (PMv). These areas are also activated during some motor responses, suggesting that they serve as the interference between multisensory integration and sensorimotor integration. Neuroimaging studies have
reported that these multisensory areas were hypoactive in PD patients (Eidelberg, 2009; Lozza et al., 2004; Ma et al., 2007; Moeller et al., 1999; Tessitore et al., 2012). A TMS study showed reduced PPC-M1 interaction in PD (Palomar et al., 2013). These results indicate that multisensory integration may be altered in PD and that the alteration may underlie the abnormal sensorimotor integration mechanisms. However, there are no neurophysiological studies examining the interaction between sensory cortices and motor cortices during multisensory integration in PD patients.

Multisensory integration can be evoked and evaluated by RHI, in which visual, tactile and proprioceptive sensory information interacts with each other, leading to an illusory feeling of ownership of a rubber hand in view and a shift in perceived position of occluded own hand towards the rubber hand. In Study One, we showed that sensorimotor integrations measured as SAI and LAI were reduced by RHI in healthy individuals. We also demonstrated that stronger RHI correlated with less facilitatory interaction between PPC and M1.

In the present study, we assessed RHI evoked by visuo-tactile-proprioceptive integration in PD patients on and off dopaminergic medications and compared it with that in age-matched HCs. We further investigated the modulations of SAI and LAI by RHI in PD patients. Finally, we analyzed the correlation between the RHI strength and the PPC-M1 interactions in PD patients. We hypothesize that: 1) RHI will be diminished in PD patients OFF medications (PD-OFF) due to impaired visuo-tactile-proprioceptive integration, 2) both SAI and LAI will be less affected by RHI in PD-OFF compared to controls due to deficits in sensorimotor integration 3) the correlation between the PPC-M1 interaction and the strength of RHI will be disrupted in PD-OFF reflecting PPC dysfunction. 4) The above deficits will be restored by dopaminergic medications in PD-ON state.

### 4.3 Methods

#### 4.3.1 Subjects
Twelve patients with PD (age 52-79, mean age ± SD 64.9±8.0 years old: 9 men and 3 women, 2 left handed and 10 right handed) and 12 age-matched HCs (age 51-77, mean age ± SD 64.1 ± 7.8 years old: 6 men and 6 women, all right handed) were tested. The data of 11HCs were included in Study One. PD patients who fulfilled the following criteria were included; diagnosed with PD based on UK PD society Bank Criteria, aged between 50 and 80 years old and stable dopaminergic medication dose over 4 weeks. PD patients either with severe tremor, severe dyskinesia, cognitive impairment, any other neurological or psychiatric diseases, medication of anti-depressants or sedatives, or history of DBS surgery were excluded. A summary of the clinical features of the PD patients are shown in Table 1. The disease duration was 7.6 ± 5.3 years. Unified Parkinson’s Disease Rating Scale (UPDRS) part III was used to assess the severity of the motor signs in “ON” or “OFF” dopaminergic medication states. The ON and OFF medication states were evaluated on separate days. For the “on” medication visit, the PD patients took their usual dopaminergic medications (PD-ON). For the “off” medication visit, they were tested after overnight withdrawal of the dopaminergic medications at least for 12 hours (PD-OFF). The presence of sensory symptoms was assessed by asking whether the patient had uncomfortable feelings in his or her body such as pain, aches, tingling or cramps over the past four weeks (adopted from question 1.9 in the UPDRS). All participants gave written informed consents and the protocol was approved by University Health Network Ethics Board.

4.3.2 Rubber Hand Illusion (RHI) and behavioral assessments

The RHI task, originally reported by Botvinick and Cohen (Botvinick & Cohen, 1998) was used in the same way with Study One. Briefly, a rubber right hand, which is in view, was set in an anatomically congruent way on a table. The participant’s actual right hand was placed lateral to the rubber hand and was occluded from the participant’s view (Figure 6A). Prior to the induction of RHI, proprioceptive judgement (PJ) reporting the right index finger position was repeated 6 times and the values were averaged and determined as the baseline position. The RHI was induced by stroking both the rubber
hand index finger and the participants' own index finger simultaneously for three minutes. The strokes of the two paintbrushes were synchronized in terms of timing and location in the synchronous condition (experimental condition), and they were out of phase in the asynchronous condition (control condition). The order of the synchronous and asynchronous conditions was randomized. PJ was repeated immediately after the induction period in each condition. At the end of each block, questionnaires that consisted of 9 statements were administered to assess the subjective experience of RHI. For each statement, the participants rated their agreement by marking on a 14 cm-long visual-analog scale (0=completely disagree, 14=completely agree).

4.3.3 Digital nerve stimulation (DNS)

Electrical stimulation was applied to the palm side of the right index finger over the distal and middle phalanx through small pad electrodes (size, 28mm x 20 mm) with cathode positioned proximally using a DS7A constant-current stimulator (pulse width 0.2ms; Digitimer, Welwyn Garden City, UK). Sensory threshold (ST) was determined as the lowest intensity felt by the participants.

4.3.4 Surface electromyography (EMG) recording

Surface electromyography (EMG) was recorded from the relaxed right first dorsal interosseous (FDI) muscle using Ag-AgCl electrodes with the active electrode on the muscle belly and the reference electrode over the right metacarpo-phalangeal joint. The EMG signals were amplified (1000 X), filtered (band pass 20 Hz-2.5kHz; Intronix Technologies Corporation Model 2024F, Bolton, Ontario, Canada), digitized at 5kHz by an analog-to-digital (A/D) interface (Micro 1401, Cambridge Electronics Design, Cambridge, UK) and stored in a laboratory computer for off-line analysis using SIGNAL software (Cambridge Electronic Devices, Cambridge, UK).
4.3.5 Transcranial magnetic stimulation (TMS)

Transcranial magnetic stimulation (TMS) was performed using a Magstim 200 stimulator (Magstim, Whitland, UK) and a custom-made figure-of-eight coil (diameter, 50 mm). The area for eliciting the best motor response in the right FDI muscle was established over the left M1 with posterior to anterior induced current direction and the coil position was marked on the scalp as the motor hot spot. The test stimulus (TS) intensity was adjusted to evoke ~ 1 mV peak-to-peak amplitude motor evoked potentials (MEPs) from the relaxed right FDI muscle. Peak-to-peak MEP amplitude for each trial was measured and averaged for each stimulation condition.

4.3.5.1 Experiment 1: Measurement of short-latency afferent inhibition (SAI) and long-latency afferent inhibition (LAI)

In Experiment 1, we assessed SAI and LAI in 12 PD patients and 12HCs. The data from eleven healthy participants who participated in the study one were included. As a conditioning stimulus, DNS was applied with the intensity of 3 times of sensory threshold (Chen et al., 1999; Sailer et al., 2003). Each run consisted of 3 different conditions: TS alone, DNS followed by TS at ISI of 23ms for SAI (DNS\textsubscript{23}-TS), and at ISI of 203 ms for LAI (DNS\textsubscript{203}-TS). These conditions were delivered in a random order and repeated 11 times with 5 seconds apart. Eleven trials for each condition (total 33 trials) were recorded at baseline and as well as immediately after the induction of RHI.

4.3.5.2 Experiment 2: Measurement of the interaction between the posterior parietal cortex (PPC) and the primary motor cortex (M1)
In Experiment 2, we assessed the PPC-M1 interaction with a paired-pulse TMS paradigm using two coils. We studied 12 PD patients and 12 age-matched healthy volunteers, 11 of whom were included in Study One. The left PPC was identified using a frameless stereotaxic neuronavigation (Brainsight Rogue Research, Canada) system. The participants’ T1-weighted magnetic resonance images (MRI) were obtained before the study visit. We obtained the MRI images from 9 PD patients and 8 HCs. The left medial superior parietal lobe (SPL) was identified based on the individual anatomical landmarks (Talairach coordinates: group mean ± SD for PD patients: \(x=-24.8\pm14.1, y=-78.1\pm12.18, z=60.6\pm16.4\): Age matched HCs: \(x=-21.4\pm6.6, y=-68.2\pm10.6, z=55.4\pm10.1\)). For those who did not have MRI images available, the CP1 in the International 10-20 electroencephalogram (EEG) system was used to locate the left SPL. Conditioning stimuli (CS) was delivered to the left PPC with posterior-anterior (PA) current direction through a 40mm figure-of-eight coil (Figure7). The TS coil was placed over the left M1 at the optimal position for the right FDI muscle (the motor hot spot). TS intensity was adjusted to evoke ~ 1 mV MEP amplitudes. The CS intensity was set at 90% of resting motor threshold (RMT), which was determined from the motor hot spot as the lowest intensity which evoked more than 50 µV peak-to-peak amplitude MEPs in 5 out of 10 consecutive trials. Each run consisted of 5 conditions with different inter-stimulus intervals (ISIs: TS alone, CS followed by TS; CS-TS at 4, 6, 8, or 10 ms of ISI) and these 5 conditions were delivered in random order with 5 seconds apart and repeated 9 times each.

### 4.3.6 Experimental Designs

We tested the modulation of SAI and LAI by RHI in Experiment 1, and that of PPC-M1 interaction in Experiment 2. These experiments were conducted either in a same day or separate days. As shown in Fig 6B, each experiment started with baseline TMS measurement followed by PJ. After RHI induction either with synchronous or asynchronous condition and post-RHI PJ, the TMS measurements were repeated. The participants kept their right hand still until the TMS measurement was completed. After
filling out the questionnaire, the participants were given a five-minute break, during which they moved their right hand to cancel the RHI effect. Then, the alternate condition was tested with the same procedure. The order of the synchronous and asynchronous conditions was randomized and counter-balanced.

4.4 Data Analysis

Statistical analysis was conducted with SPSS 17.0 and significance was set at P < 0.05 unless otherwise stated. Kolmogotov-Smirov normality tests were performed to test normal distributions. If the values were not distributed normally, non-parametric tests were used. Otherwise, parametric tests were performed.

4.4.1 Clinical Assessments

The severity of motor signs was assessed by UPDRS scores part III and the scores in the “ON” medication state (PD-ON) and “OFF” medication state (PD-OFF) were compared by paired-t test.

4.4.2 RHI Behavioural Assessments

The results from the first sets of synchronous and asynchronous conditions were used to assess the strength of RHI at the behavioral level except for the correlation analysis in the Experiment 2 in which the concurrent RHI experience was used to examine the relationship between behavioural results and neurophysiological changes.

4.4.2.1 Evaluation of the Questionnaire
The scores for the first three statements in the questionnaire (Q1-3) were added and averaged in synchronous or asynchronous condition separately in each participant. The RHI induction was examined by comparing the synchronous score with asynchronous score using the paired t-test in each group. To evaluate the influence of dopaminergic medications in PD patients, two-way repeated ANOVA was conducted with CONDITION (Synchronous vs Asynchronous) and MEDICATION (ON vs OFF) as two separate repeated measures. In order to compare the RHI strength in PD patients with age-matched HCs, separate repeated measures ANOVA were performed with CONDITION (Synchronous vs Asynchronous) as within subject factor and GROUP (PD “ON” patients vs HCs, or PD “OFF” patients vs HCs) as between subject factor. Significant main effects were further investigated by post-hoc paired t tests with Bonferroni correction.

4.4.2.2 Evaluation of the Proprioceptive judgment (PJ) task

The shift in the estimated position of own right index finger after the RHI induction (arm shift) was computed by subtracting the baseline PJ value from the post induction PJ value in each condition for individual participant. To compare PD patients with HCs, two-separate ANOVAs were performed with GROUP (PD-ON vs HCs, or PD-OFF vs HCs) as a between-subject factor and CONDITION (Synchronous vs Asynchronous) as within-subject factor. The contribution of the dopaminergic medications was analyzed by a separate two-way repeated measures ANOVA with MEDICATION (ON vs OFF) and CONDITION (Synchronous vs Asynchronous) as two repeated measures.

4.4.3 Assessment of Transcranial magnetic stimulation (TMS) Measurements

4.4.3.1 Experiment1: The modulation of Short-latency afferent inhibition (SAI) and Long-latency afferent inhibition (LAI) by RHI
As described in Study One, SAI and LAI were expressed as a ratio of the conditioned (DNS$_{23}$-TS, DNS$_{203}$-TS) to the unconditioned (TS alone) MEP amplitudes. Ratios <1 indicate inhibitory and ratios > 1 indicate facilitatory influences of DNS to M1.

First, we examined the alteration of SAI at baseline by comparing the baseline SAI in PD-ON or PD-OFF with that in HCs using two-tailed t-test. Secondly, the modulation of SAI by RHI in HCs and PD patients were analyzed using two separate two-way repeated ANOVAs with CONDITION (baseline, sync, async) as within-subject factor and GROUP (HC, PD-ON/OFF) as between-subject factor. Thirdly, the effect of dopaminergic medications on SAI in PD patients at baseline was assessed by comparing PD-ON and PD-PFF with paired t-test. Then, the overall dopaminergic medication influence was analyzed by another repeated measures ANOVA with MEDICATION (ON and OFF) and CONDITION as two separate repeated measures. The same analysis was performed for LAI. In addition, the baseline LAI ratio was subtracted from the post induction LAI ratio (delta LAI) in each condition to further investigate the LAI modulation by RHI. The delta LAI values for PD-ON or OFF group was compared with that for HCs using repeated measures ANOVA with factor CONDITION (synchronous, asynchronous) as within-group factor and GROUP (HCs vs PD-ON/OFF) as a between-group factor. Significant main effects were followed up by paired t tests with Bonferroni adjustment.

### 4.4.3.2 Experiment2: The modulation of Posterior parietal cortex (PPC)-Primary motor cortex (M1) interaction by RHI

The MEP amplitudes at each ISI were expressed as a ratio of the conditioned (CS-TS at ISI 4, 6, 8, and 10 ms of ISIs) to the unconditioned (TS alone) MEP amplitudes. Ratios <1 indicates inhibitory and ratios > 1 indicates facilitatory influence of PPC to M1 at the specific ISI. First, the baseline PPC-M1 interaction in the PD patients and the HCs were compared using two separate repeated measures ANOVA with ISI (4, 6, 8, and 10 ms) being a within-subject factor and GROUP (PD-ON vs HCs or PD-OFF vs HC) being a
between–subject factor. Secondly, the modulation of PPC-M1 interaction by RHI in synchronous condition was analyzed by comparing PD patients with HCs using two separate repeated measures ANOVA with ISI (4, 6,8, and 10 ms) being a within-subject factor and GROUP (PD-ON vs HCs or PD-OFF vs HC) being a between–subject factor. Thirdly, the same analysis was conducted for asynchronous condition. Any significant main effects in these ANOVA tests were followed by post-hoc paired t-test with Bonferroni correction.

In addition, the relationship between the strength of the RHI and the PPC-M1 interaction was analyzed. The MEP ratios in synchronous condition were averaged across different ISIs in each individual because there were no significant differences among ISIs in Study One. The relationship between the averaged Q1-3 scores in Experiment 2 and the averaged MEP amplitude in each group (PD-ON, PD-OFF, and HCs) was analyzed separately using Pearson correlation.

### 4.5 Results

#### 4.5.1 Clinical and demographic data

Table 1 shows the patients’ demographics, the scores for the UPDRS part III for ON or OFF medication states as motor features and the scores for the sensation related question as sensory symptoms. Three patients showed predominant motor symptoms on the right side and 9 patients on the left side. The types of the predominant motor symptoms were tremor in 5 patients (tremor type) and rigidity and bradykinesia in 7 patients(akineti rigid type). Paired t-test showed that the UPDRS scores for the ON visit was significantly lower than that for the OFF visit (p<0.001) confirming the clinical benefits of dopaminergic medications on the motor symptoms.
### Table 1 Patients demographic Characteristics

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<th>Disease</th>
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<th>UPDRS</th>
<th>LED (mg/day)</th>
<th>Sensory</th>
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**Table 1**

H&Y: Hoehn and Yahr scale, Gender F: female, M: male, Predominant side: the side of the predominant motor symptoms, Predominant symp: types of the predominant motor symptoms, T: tremor, AR: akinetic rigid type, UPDRS: Unified Parkinson’s rating scale, LED: levodopa equivalent dosage of dopaminergic medications, Sensory: score for question 1.9 in UPDRS
4.5.2 Behavioural assessments of Rubber Hand Illusion

4.5.2.1 Questionnaire on the rubber hand illusion experiences

The scores of agreements to statements 1-3 (Q1-3: the RHI related experiences) for the synchronous and asynchronous conditions in each group are shown in Figure 11A. We found that there was no difference in the level of RHI between PD patients and age-matched HCs (HC) groups and that the dopaminergic medication did not influence subjective feeling of RHI. In age-matched healthy population, the synchronous condition scored significantly higher than the asynchronous condition ($t(11)=3.68$, $p=0.004$), indicating successful induction of the RHI. PD patients in both ON and OFF medication states also showed significant difference between the synchronous and asynchronous scores (PD-OFF: $t(11)=5.468$, $p=0.0002$, PD-ON: $t(11)=3.583$, $p=0.0043$). Two-way repeated ANOVA comparing PD-ON and OFF showed that there was an overall main effect of Condition ($F(1,11)=22.7$, $p=0.001$) with no main effect of Medication ($F(1,11)=0.04$, $p=0.85$) or no interaction between Medication and Condition ($F(1,11)=3.91$, $p=0.07$). Two-way ANOVA comparing PD-ON versus HC revealed an overall main effect for Condition ($F(1,22)=25.93$, $p<0.01$), no significant main effect of Group ($F(1,22)<0.001$, $p=0.99$) and no Condition by Group interactions ($F(1.22)=0.295$, $p=0.59$). Similarly, comparison between PD-OFF versus HC also revealed an overall main effect for Condition ($F(1,22)=42.75$, $p<0.001$), no significant main effect of Group ($F(1,22)=0.016$, $p<0.90$) and no Condition by Group interactions ($F(1.22)=2.82$, $p=0.11$).

4.5.2.2 Proprioceptive judgment (PJ)

The shifts in perceived hand position in each group are shown in Figure 11B. We found that no significant difference in the shift between PD group and HC. Dopaminergic medication did not influence PJ in PD patients. Two-way ANOVA comparing PD-ON and HC showed no main effect of Group ($F(1,22)=0.63$, $p=0.44$), no main effect of Condition ($F(1,22)=1.29$, $p=0.27$), and no interaction between Condition and Group.
(F(1,22)=0.03, p=0.87). Comparison between PD-OFF and HC also showed no main effect of Condition (F(1,22)=1.69, p=0.21), no main effect of Group (F(1,22)=0.63, p=0.44) and no interaction between Condition and Group (F(1,22)=2.13, p=0.16). The influence of dopaminergic medication was analyzed by two-way repeated ANOVA which showed no main effect of Medication (F(1,11)=1.22, p=0.29), no main effect of Condition (F(1,11)=2.08, p=0.18), or no significant interaction between Medication and Condition (F(1,11)=0.23, p=0.64).
**Figure 11 Behavioral Results in PD patients and HCs**

**A. Questionnaire Results**

- The X axis denotes the average score for the first to the third statements in the questionnaire.
- The average of the first three statements (Q1-3) in the synchronous condition were scored higher than the asynchronous condition in HC, PD-OFF and PD-ON. All of them were scored to the similar degrees.

**B. Proprioceptive Judgment**

- Shift in hand position, shown in Y-axis, was calculated by subtracting the baseline hand position from the post RHI position.
- There were no significant differences between HCs and PD-OFF or PD-ON.
- The dopaminergic medication did not influence PJ. Error bars indicate standard errors of means (SEM).

**Figure 11 A) Questionnaire results showing subjective experience of RHI.** X axis denotes the average score for the first to the third statements in the questionnaire. The average of the first three statements (Q1-3) in the synchronous condition were scored higher than the asynchronous condition in HC, PD-OFF and PD-ON. All of them were scored to the similar degrees. **B) Proprioceptive judgment in each group.** Shift in hand position, shown in Y-axis, was calculated by subtracting the baseline hand position from the post RHI position. There were no significant differences between HCs and PD-OFF or PD-ON. The dopaminergic medication did not influence PJ. Error bars indicate standard errors of means (SEM). S:synchronous, A:asynchronous, HC: age-matched HCs, PD-OFF: PD patients with OFF medication, PD-ON: PD patients with ON medication.
4.5.3 Modulation of short-latency afferent Inhibition (SAI) by Rubber Hand Illusion

4.5.3.1 Comparison between Parkinson’s Disease Patients and Healthy Controls

Figure 12 shows the modulation of SAI by RHI in each group. We found that PD-OFF showed overall reduction in SAI compared to HC. T-test showed that SAI at baseline in PD-OFF was not statistically different from HC (t(22)=-0.007, p=0.99). Two-way ANOVA comparing PD-OFF and HC revealed a significant main effect of Group (F(1,22)=4.87, p=0.038), but no main effect of Condition (F(2,44)= 1.91, p=0.16) or the interaction between Condition and Group (F(2, 44)=1.08, p=0.35). The comparison between PD-ON with HC by t-test showed that SAI at baseline in PD-ON was not different from HC (t(22)=-0.985, p=0.34). Two-way ANOVA comparing PD-ON and HC showed no main effect of Condition (F(2,44)=0.09, p=0.91), no main effect of Group (F(1,22)=0.75, p=0.40) or no significant interaction between Condition and Group (F(2,44)=2.02, p=0.14).

4.5.3.2 Dopaminergic Influence on the SAI modulation in Parkinson’s Disease Patients

Paired t-test showed that SAI at baseline was not different between PD-ON and PD-OFF (t(22)=0.90, p=0.39). Two-way repeated ANOVA comparing PD-ON and PD-OFF showed no main effect of Medication (F(1,11)=1.18, p=0.30), or no main effect of Condition (F(2,22)=1.30, p=0.29) or no interaction between Medication and Condition (2,22)=1.22, p=0.32).
Figure 12 Modulation of Short-latency Afferent Inhibition by RHI in PD patients and HCs

Modulation of Short-latency afferent inhibition (SAI) in HCs, PD-OFF and PD-ON patients. Y axis denotes the ratio of the conditioned to unconditioned MEP amplitude. The ratio >1.0 indicates facilitatory and the ratio <1.0 indicates inhibitory influence of DNS over M1 at short-latency (23ms). Baseline SAI in each group was not significantly different each other. Overall SAI was significantly reduced in PD-OFF patients compared to HCs. Error bars represents standard error of the mean. B: baseline, S:synchronous, A:asynchronous, HC: age-matched HCs, PD-OFF: PD patients with OFF medication, PD-ON: PD patients with ON medication.
4.5.4 Modulation of Long-latency afferent Inhibition (LAI) by Rubber Hand Illusion

4.5.4.1 Comparison between Parkinson’s Disease Patients and Healthy Controls

A-priori t-test showed significant reduction of baseline LAI in PD-OFF patients compared to HC (t(22)=-2.03, p=0.055 for PD-OFF). Baseline LAI in PD-ON was not significantly different from HC (t(22)=-1.86, p=0.076).

The modulation of LAI by RHI in each group is shown in Figure13A. We found that LAI in synchronous condition was increased in PD-ON while it was decreased in HC. The comparison of PD-ON with HC using two-way ANOVA showed significant interaction between Condition and Group (F(2,44)=5.21, p=0.009), with no main effect of Condition (F(2,44)=1.64, p=0.21) or Group (F(1,22)=0.52, p=0.48). Post hoc analysis showed that synchronous LAI in HC was significantly reduced compared to either baseline (p=0.038) or the asynchronous condition (p=0.0089) in HC but not in PD-ON (sync vs baseline: p=0.10, sync vs async p=0.94). In order to investigate the RHI modification of LAI further, LAI change from the baseline in each condition in PD-ON patients was compared to HC (Figure 13B). We confirmed the altered modulation of LAI in PD-ON. Two-way ANOVA showed significant main effect of Group (F(1,22)=6.06, p=0.022) with significant interaction between Group and Condition (F(1,22)=4.63, p=0.043). There was no significant main effect of Condition (F(1,22)=2.21, p=0.15). We did not find any difference between PD-OFF and HC (Figure 13A). Two-way ANOVA comparing PD-OFF with HC revealed no significant effect of Group (F(1,22)=3.558, p=0.07), Condition (F(2,44)=1.21, p=0.31) or Condition by Group interaction (F(2,44)=0.57, p=0.57).

4.5.4.2 Parkinson’s Disease Patients and the Effect of Dopaminergic Medications
As figure 13A shows, there was an overall reduction in LAI in PD-OFF compared to PD-ON. LAI at baseline in PD-ON and OFF medication was compared by paired t-test which showed no statistical difference (t(11)=-0.65, p=0.53). Two-way repeated ANOVA comparing PD-ON and PD-OFF demonstrated a significant main effect of Medication (F(1,11)=8.87, p=0.013), but no main effect of Condition (F(2,22)=0.20, p=0.82) or Medication by Condition interaction (F(2,22)=0.94, p=0.41).
Figure 13 Modulation of Long-latency Afferent Inhibition in PD patients and HCs

**Figure 13A.** Modulation of LAI. Y axis denotes ratio of the conditioned to unconditioned MEP amplitude. Ratios > 1.0 indicate facilitatory and ratios < 1.0 indicate inhibitory influence of DNS over M1 at long-latency (203 ms). Baseline LAI was significantly reduced in PD-OFF compared to HCs. Overall LAI was also reduced in PD-OFF compared to PD-ON. When PD-ON was compared to HC, there was a significant interaction between Condition and Group suggesting that LAI was modulated differently in PD-ON compared to HC. Error bars represents standard error of the mean (SEM). B: baseline, S: synchronous, A: asynchronous, HC: age-matched HCs, PD-OFF: PD patients with OFF medication, PD-ON: PD patients with ON medication. **13 B** Change in LAI from the baseline. Baseline value for LAI was subtracted from post induction LAI.
are plotted. In synchronous condition, LAI was reduced from the baseline in HC while it was increased in PD-ON confirming that RHI abnormal modulation of LAI in PD-ON. Error bars indicates standard error of the mean (SEM).
4.5.5 Modulation of PPC-M1 interaction by RHI

4.5.5.1 Comparison between Parkinson’s Disease Patients and Healthy Controls

Figure 14A shows the baseline PPC-M1 interaction in each group. There was no significant difference among the three group. Two-way ANOVA comparing PD-OFF with HCs showed that there was no significant main effect of Group (F(1,22)=3.52, p=0.07) or ISI (F(3,66)=0.38, p=0.77), and no interaction between Group and ISI (F(3,66)=0.19, p=0.90). Similarly, the comparison between HCs and PD-ON with two-way ANOVA showed no significant main effect of Group (F(1,22)=0.97, p=0.34) or ISI (F(3, 66)=1.36, p=0.26), and no Group by ISI interaction (F(3,66)=0.93, p=0.43).

PPC-M1 interactions in the synchronous condition are shown in Figure 14B. Comparison between PD-OFF and HC by two-way ANOVA showed no significant main effect of Group (F(1,22)=1.12, p=0.30) or ISI (F(3,66)=1.55, p=0.21), and no significant interaction between Group and ISI (F(3, 66)=0.38, p=0.77). Two-way ANOVA comparing PD-ON with HCs showed that there was no significant main effect of Group (F(1,22)<0.001, p>0.99) or ISI (F(3,66)=0.27, p=0.85), and no Group x ISI interaction (F(3,66)=1.00, p=0.40).

In the asynchronous condition (Figure 14C), PD-OFF was compared with HC using two-way ANOVA showed no significant main effect of Group (F(1,22)=0.35, p=0.56) or ISI (F(3,66)=0.85, p=0.47), nor Group x ISI interaction (F(3,66)=2.59, p=0.06). Comparison between PD-ON and HC revealed a significant main effect of ISI (F(3,66)=3.34, p=0.024). There was no significant main effect of Group (F(1,22)=0.005, p=0.95) nor ISI x Group interaction (F(3,66)=0.88, p=0.46). Post hoc analysis showed that PPC-M1 interactions at 8 ms (p=0.041) and 10 ms (p=0.02) ISIs were more facilitated than 4 ms ISI in HC and PD-ON patients (Figure 13C).
4.5.5.2 The Effect of Dopaminergic Medications in Parkinson’s Disease Patients

The influence of dopaminergic medications on PPC-M1 interaction at baseline (Figure 14A) was analyzed by two-way repeated ANOVA which showed no significant main effect of Medication ($F(1,11)=0.051$, $p=0.83$) or ISI ($F(3,33)=0.55$, $p=0.65$). There was no interaction between Medication and ISI ($F(3,33)=1.22$, $p=0.32$). In the synchronous condition, there was no significant main effect of Medication ($F(1,11)=1.02$, $p=0.34$), ISI ($F(3,33)=0.45$, $p=0.72$) or no interaction between Medication and ISI ($F(3,33)=1.28$, $p=0.30$). In the asynchronous condition, two-way repeated ANOVA showed no significant main effect of Medication ($F(1,11)=0.31$, $p=0.59$), ISI ($F(3,33)=0.98$, $p=0.41$) and interaction between Medication and ISI ($F(3,33)=1.56$, $p=0.22$).
Figure 14 Modulation of PPC-M1 interaction by RHI

A. PD patients vs HC for PPC-M1 interaction at baseline

B. PD patients vs HC for PPC-M1 interaction in Sync

C. PD patients vs HC for PPC-M1 interaction in Async
Figure 14 A) PPC-M1 interaction at baseline. PPC-M1 interaction is expressed as a ratio of the conditioned to unconditioned MEP amplitudes and is shown in the Y-axis. The X-axis denotes 4 different ISIs, 4, 6, 8 and 10 ms. The ratios < 1 indicate inhibitory, and the ratios > 1 indicate facilitatory influence of PPC over M1. PPC-M1 interaction at baseline was similar between PD and HC. B) PPC-M1 interaction in the synchronous condition. Modulation of PPC-M1 interaction by RHI was similar in HC and PD patients. The dopaminergic medications did not influence the way RHI modulated the PPC-M1 interaction. C) PPC-M1 interaction in the asynchronous condition. No difference was found between PD and HC in the asynchronous condition. PPC-M1 interaction overall was more facilitated at 8 ms and 10 ms ISI compared to 4 ms ISI. Error bars denotes standard error of means (SEM).
4.5.5.3 Correlation between the Strength of RHI and PPC-M1 Interaction

Figure 15 shows the relationship between the strength of RHI experience and the modulation of the PPC-M1 interactions by RHI in controls, PD-OFF and PD-ON group. We found that the negative correlation in HC was lost in PD patients suggesting deficits in PPC-M1 interaction in PD patients regardless of medication status. In HC, the average score for Q1-3 negatively correlated with the average MEP amplitude across 4-10ms ISI in synchronous condition ($r^2=0.40$, $p=0.028$). The result indicates that stronger RHI experience is associated with more inhibitory PPC-M1 interaction. In PD-OFF, the average Q1-3 score did not correlate with the MEP amplitudes in the synchronous condition ($r^2=0.118$, $p=0.28$). The correlation between the average Q1-3 and the averaged MEP amplitude was not restored in PD-ON ($r^2=0.085$, $p=0.78$).
Figure 15 Correlations between RHI Strength and PPC-M1 interactions

Figure 15. Correlation between the level of RHI experience and PPC-M1 interaction in the synchronous condition in HCs (HC:top), PD-OFF(middle) and
**PD-ON (bottom).** The PPC-M1 interaction is expressed as an average MEP amplitudes ratio across 4-10 ms ISIs in the synchronous condition. The Y-axis represents the average ratio of the amplitude of the conditioned to unconditioned MEPs. The ratios>1 indicate facilitatory, and the ratios<1.0 indicate inhibitory influence of PPC over M1. X-axis denotes the average score for the first three statements in the questionnaire in the synchronous condition. In HCs, there was a negative correlation between the average MEP ratio and average score for the first three statements, indicating that greater inhibitory PPC-M1 interactions were associated with stronger RHI experience.
4.6 DISCUSSION

In the current study, we investigated whether multisensory integration evoked by RHI was different in PD patients compared to HC at the behavioural level. The behavioural result revealed that the visuo-tactile integration was preserved in PD patients. In Experiment 1, we examined modulation of SAI and LAI by RHI to assess how sensorimotor integration was influenced by the RHI-induced visuo-tactile integration. We found that SAI was reduced overall in PD patients in the OFF-medication state compared to HC. LAI in PD patients was found to be reduced in the OFF compared to ON medication state, suggesting that dopaminergic medications influence LAI. LAI was differently modulated by RHI in PD-ON compared to HC. LAI in the synchronous condition was increased in PD-ON while it was decreased in HC. In Experiment 2, the association between the strength of RHI and the inhibitory PPC-M1 interactions observed in HC was not observed in PD patients regardless of dopaminergic medication states, suggesting that the functional connectivity between PPC and M1 is disrupted in PD.

4.6.1 Preserved RHI at the Behavioural Level in PD patients

Similar with HC, PD patients exhibited stronger feeling of RHI experiences assessed by questionnaire in the synchronous condition than the asynchronous condition. The result showed that there was no significant difference in the extent of the subjective feeling of RHI between PD patients and HC, indicating that PD patients are able to integrate vision and tactile inputs relating to own hand. We also demonstrated that dopaminergic medications did not modulate the strength of RHI in PD. In a previous study, patients with dystonia showed normal pattern of subjective RHI experience (Fiorio et al., 2011). Therefore, both PD and focal hand dystonia patients have the ability to integrate vision with tactile inputs relating to RHI. Proprioceptive shift occurs as a result of multisensory integration in which more reliable vision dominates over proprioception (Botvinick & Cohen, 1998). Our results showed that proprioceptive judgment in PD patients was also
comparable to that in HC regardless of dopaminergic medication states. Patients with focal hand dystonia showed reduced proprioceptive shift after RHI while they still experienced subjective RHI (Fiorio et al., 2011). The selective impairment of proprioceptive arm shift without lack of subjective experience of RHI may indicate the failure of reducing the weight of proprioceptive inputs during multisensory integration. The reduced proprioceptive shift in focal hand dystonia was presumed to be associated with proprioceptive deficits (Fiorio et al., 2011). Although previous studies also reported proprioceptive deficits in PD (Maschke et al., 2003; O'Suilleabhain et al., 2001; Zia et al., 2000; Zia et al., 2002), we did not find any difference in the proprioceptive arm shift between PD patients and HC. The underlying mechanism of proprioceptive deficits in PD is likely different from that in focal hand dystonia. In previous studies, proprioceptive deficits in PD or dystonia have been examined in tasks that required arm movements (Avanzino & Fiorio, 2014; Maschke et al., 2003; O'Suilleabhain et al., 2001; Zia et al., 2000; Zia et al., 2002) and therefore the deficits may reflect proprioceptive-motor integration rather than proprioception as perception. Proprioceptive judgment in our study only involves the multisensory systems but not the motor system, and thus enables us to separate proprioceptive-motor integration from visuo-tactile-proprioceptive integration. One possibility is that proprioceptive deficiency in PD patients may arise from alterations in the link between the sensory and motor systems (proprioceptive-motor integration) while that in focal hand dystonia may resulted from altered multisensory integration of vision, tactile and proprioceptive perceptions. Another possibility is that visual dominance in PD patients might have compensated for the proprioceptive deficits. During RHI in healthy participants, a mismatch between visuo-tactile and proprioceptive inputs compromises the vague proprioceptive inputs from own hand and enforces visual inputs. As a result, the weight of the proprioceptive inputs is reduced and the weight of the visual inputs are increased, leading to proprioceptive arm shift towards the rubber hand. Because PD patients have been reported to rely more on vision than proprioception (Jobst et al., 1997; Konczak et al., 2009; Martens & Almeida, 2012), they already have visual over-reliance and compromised proprioception before
the induction of RHI begins. Their visual over-reliance might have concealed the possible deficits in RHI induced multisensory integration.

4.6.2 Overall Reduction in SAI in PD-OFF Compared to HCs

SAI at baseline in PD patients did not differ from HC regardless of dopaminergic medication states. Although it was reported in previous study that SAI was reduced at rest in PD-ON but not in PD-OFF when MNS was used (Sailer et al., 2003), the same study reported that SAI elicited by DNS did not show this finding.

When PD-OFF patients were compared with HCs, SAI overall was significantly reduced. As there was no significant main effect of Condition or Group x Condition interaction, the SAI reduction was not likely specific to RHI. However, considering that there was no difference in SAI at baseline between the two groups, the reduced SAI in PD-OFF medication might have evoked by the sensory stimuli in the both synchronous and asynchronous conditions, such as visual or tactile, or both inputs. In other words, the reduced SAI in PD-OFF may be more pronounced when visual and tactile sensory stimuli were applied compared to without these additional stimuli.

We did not see any significant differences in overall SAI between PD-ON patients and HC. This may seem to conflict the previous result showing reduced SAI in PD-ON medication but normal SAI in PD-OFF medication (Sailer et al., 2003; Wagle Shukla et al., 2013). However, several technical differences might lead to the different results.

Firstly, the disease severity of the tested hand might have been different in our study and the past studies. In the previous studies, SAI was tested on the more affected side while our study tested SAI in the right hand regardless of the side of the more affected hand. In fact, nine out of twelve of our patients were tested in the less affected hand.

We tested the right hand because previous studies which showed the involvement of parietal cortex in RHI tested the left hemisphere (Ehrsson et al., 2004; Kammers, Verhagen, et al., 2009) and there maybe hemispheric specialization of PPC functions (Kessels, d'Alfonso, Postma, & de Haan, 2000; Vesia & Crawford, 2012). In order to
examine the left PPC-M1 interactions, the right hand was chosen for the induction of RHI. Secondly, the technique to evoke SAI was different. MNS was stimulated at the wrist in the previous studies while our study used DNS, with which a previous study reported no significant reduction of SAI in PD-ON patients (Sailer et al., 2003). SAI by DNS is not as pronounced as SAI by MNS. In addition, SAI was measured at rest in previous studies while we measured SAI not only at rest but also during RHI.

As SAI is likely to represent a direct interaction between S1 and M1, the reduced SAI in PD-OFF may represent the reduction in the connection between S1 and M1 relating to sensory stimuli. A neuroimaging study in PD patients reported impaired S1 activation during a coin rotation task, which was not affected by dopaminergic medications (Foki et al., 2015). Reduced M1 and S1 activities were reported during tactile stimulation in a fMRI study in PD-OFF patients (Cao, Xu, Zhao, Long, & Zhang, 2011; B. Weder et al., 2000). The reduced SAI in our study may reflect reduced activation in S1 after tactile stimulation.

4.6.3 Reduced modulation in LAI in PD- OFF patients and Tactile-motor Integration Improvement by Medication

Baseline LAI in PD-Off was reduced compared to HC while that in PD-ON showed non-significant trend of reduction. Our results were consistent with a previous study that showed reduction in LAI in PD patients regardless of dopaminergic medication states (Sailer et al., 2003).

There was an overall reduction in LAI in PD-OFF compared to PD-ON. Comparison between PD-ON and HC showed a significant Group x Condition interaction in LAI modulation by RHI. The result indicates that dopaminergic medications might have influenced the way RHI modulated LAI. In HC, LAI was disinhibited only in the synchronous condition but not in the asynchronous condition, suggesting that the disinhibition of LAI was associated with RHI. In PD-ON, LAI was increased compared to baseline both in the synchronous and asynchronous conditions. LAI change from
baseline also showed the significant interaction between Group and Condition suggesting that the LAI modulation by RHI in the synchronous condition was abnormally increased in PD-ON patients. While the mechanisms of LAI and this abnormal modulation of LAI by RHI in PD-ON are not known, we speculated that LAI may involve both basal ganglia and cortical association areas. The reduced LAI in the synchronous condition in HC may represent a mechanism to resolve the conflict between somatosensory inputs and visual inputs by reducing the weight of the conflicting somatosensory inputs. This conflict-resolving mechanism may occur at cortical association areas. PD-ON showed increase in LAI rather than reduction during the conflict-resolving process. The result may imply the altered function in cortical association areas in PD-ON. In addition, increased LAI in PD-ON may also reflect improved tactile processing at basal ganglia level. LAI was restored by STN-DBS, indicating the involvement of the basal ganglia in LAI (Wagle Shukla et al., 2013). It has been proposed that altered tactile processing in PD patients can be attributed to abnormalities in the basal ganglia (Conte et al., 2013) and several studies showed that dopaminergic medications improved tactile processing (Artieda et al., 1992; Conte et al., 2010; Shin et al., 2005). We speculated that the better tactile processing may increase LAI in PD-ON, however, the function in cortical association areas, which supposed to detect the conflict and decrease LAI, may remain altered in PD-ON, leading to the different LAI modulation by RHI. Despite the altered modulation of LAI by RHI in PD patients, they experienced RHI to the similar extent as HC, suggesting that cortical association areas not involved in LAI may compensate to solve the conflict and to evoke the ownership feeling. Another possibility is that the areas involved in LAI are also activated by RHI, but the altered modulation of LAI by RHI in PD-ON may not lead to changes in RHI experience.

4.6.4 Disrupted PPC-M1 interaction in PD patients

PPC is one of the cortical association areas that integrates multisensory information. We showed that greater inhibitory projection from PPC to M1 was associated with
stronger RHI experience in HC. We also demonstrated the disruption of this association in PD patients regardless of dopaminergic medications, suggesting the abnormality in PPC-M1 interaction involved in RHI. Our findings support a previous TMS study which showed impaired PPC-M1 functional connectivity at rest in PD patients using the paired-pulse TMS paradigm (Palomar et al., 2013). In this report, less impaired PPC-M1 functional connectivity was associated with faster reaction time, suggesting that this functional connectivity is related to motor function. We did not find significant difference in PPC-M1 interaction at rest between HC and PD patients. This may be due to the difference in the functions of different subdivisions in the PPC. We stimulated SPL while IPL was targeted in the previous study (Palomar et al., 2013). Our study indicates that the disruption in PPC-M1 interaction in PD patients is not limited to IPL but also includes SPL. The disruption of PPC-M1 interactions in PD could be due to the altered PPC function. As PD patients showed normal RHI, they may have activated cortical areas other than PPC for multisensory integration for RHI to compensate the disrupted parieto-motor circuits. Imaging studies showed increased activation of the cerebellum and premotor area in PD (Sabatini et al., 2000; Tessitore et al., 2012; Wu & Hallett, 2005). These areas may compensate for the PPC dysfunction in PD patients to integrate multisensory inputs. Alternatively, changes in the subcortical white matter connections between PPC and M1 may lead to the disrupted PPC-M1 interaction.

4.6.5 Limitation of the Study

The study has several limitations.

First, the behavioural measurement of RHI might not be sensitive enough to observe the abnormal multisensory integration in PD. While RHI is visuo-tactile integration, other types of multisensory integration such as visuo-proprioceptive integration or tactile-proprioceptive integration may be affected in PD.

Another limitation is related to the complicated mechanism of RHI. Multiple brain areas across the cerebral cortices seem to be involved in the experience of RHI. We did not
test cortical areas other than PPC which may be abnormal in PD. The majority of projections from PPC go to M1 via the premotor areas, and the premotor area may be disrupted in PD.

The pathway mediating LAI remains unclear and we could not determine the locations where the sensorimotor integration process was disrupted in PD. Further studies investigating cortical association areas and the basal ganglia using techniques such as EEG/MEG source localization or functional MRI during RHI in PD patients may be helpful.

Lastly, the RHI behavioural and neurophysiology results did not correlate with UPDRS scores. Therefore, the clinical relevance of the deficits shown in the current studies remains unclear. UPDRS may not be sensitive enough to detect correlations with our findings, which may relate to non-motor rather than motor features of PD. In addition, we tested only the right hand for RHI behavioral study and the left hemisphere for the neurophysiological studies. The majority of the patients had the left side as the more affected side. Future study can test both hands and both hemispheres.

4.7 Conclusions

The current study showed normal visuo-tactile- integration in PD patients at the behavioural level. However, our neurophysiological studies revealed abnormal sensorimotor integration while utilizing multisensory inputs in PD patients. The abnormal sensorimotor integration pathways in PD patients may involve in cortical association areas including PPC which functionally interacts with M1.
5 GENERAL DISCUSSION

5.1 Summary of Results

Study One examined how RHI, a method to induce visuo-tactile integration, modulates the integration between sensory and motor systems in HC. The main results of the studies are: 1) RHI reduced sensorimotor integration measured by SAI and LAI in healthy participants and 2) Stronger RHI experience was correlated with greater inhibitory PPC-M1 interaction in healthy participants. The reduction in SAI by RHI may indicate a diminished gain of somatosensory inputs to S1 due to the conflict between vision and proprioceptive/tactile inputs. The reduction in LAI by RHI likely also reflects modulation of somatosensory inputs in cortical association areas such as PPC, where multisensory inputs are integrated. Using these methods established in Study One, Study Two compared PD patients with age-matched HC. We demonstrated that 1) PD patients showed RHI experience to a similar degree as age-matched HC at the behavioural level, 2) PD-ON showed increase in LAI after RHI while LAI was decreased in HCs, suggesting that RHI activated multisensory and sensorimotor integration pathways differently compared to control participants and 3) PD patients lost the association between the strength of RHI and the inhibitory PPC-M1 interactions regardless of the medication status.

5.2 Normal Perception of Rubber Hand Illusion in PD Patients at the Behavioural Level

We evaluated the level of RHI using a questionnaire. Q1 asked the ownership of the rubber hand; #1. I felt as if the rubber hand were my own hand. Q2 and Q3 asked the relocation of the touch; #2. It seemed as if I were feeling the touch of the paintbrush in the location where I saw the rubber hand touched, #3. The touching of the rubber hand
felt just like an actual touch. Experiencing ownership of a rubber hand requires both multisensory integration (Botvinick & Cohen, 1998; Makin et al., 2008; Tsakiris & Haggard, 2005) and higher-level of cognitive process of judgment in which the appearance of the rubber hand is compared with participants’ own body image stored in the brain (Kilteni et al., 2015; Tsakiris, 2010). When the rubber hand appearance is realistic and there is simultaneous tactile stimulation from the own hand with visual capture of the paintbrush stroke on the rubber hand, the rubber hand will be incorporated into the subject's own body image, leading to ownership of the rubber hand. Relocation of the touches of the paintbrush from own hand to rubber hand occurs when the simultaneous visual and tactile stimuli reinforce the RHI, leading to compromising incongruent proprioceptive inputs, which inform the origin of the tactile inputs. Therefore, the average score for these three questions reflects dominated visuo-tactile integration and reduced weight of proprioception. Because there was no significant difference between HC and PD patients in these questionnaire scores, higher level of sensory processing as well as visual-tactile integration accompanied by reduced gain of proprioception appear to be intact in PD patients.

Another way of evaluating RHI was PJ, in which we measured how much the participants perceived their own hand position towards the rubber hand. It examined more specifically the reduced gain of proprioceptive inputs in the multisensory integration due to the conflict. Because this process involves proprioception, the PJ result in PD patients is of interest. Regardless of medication status, PJ in PD patients did not differ from the results in age-matched HC. Proprioception or proprioceptive-motor integration has been reported as defective in PD patients, especially without vision (Jobst et al., 1997; Konczak et al., 2009; Martens & Almeida, 2012), suggesting compensation of proprioception by visual inputs. We need to distinguish proprioceptive-motor integration from proprioception. Previous experiments used kinematic movements of arm or fingers to assess proprioception (Flash et al., 1992; Jobst et al., 1997; Konczak et al., 2009; Maschke et al., 2003; O’Suilleabhain et al., 2001; Zia et al., 2000; Zia et al., 2002), and therefore, they evaluated proprioceptive-motor integration. On the other hand, PJ in our study likely represents perceptive aspect of proprioception, rather
than proprioceptive-motor integration. Normal PJ in PD patients may support the hypothesis that the proprioceptive deficit in PD patients reported in the previous studies can be attributed to proprioceptive-motor integration deficits rather than perception in proprioception.

5.3 The effect of RHI on Short-latency Afferent Inhibition in Healthy individuals and PD patients

Study One with healthy individuals showed significant reduction of SAI in the synchronous condition but not in the asynchronous condition compared to baseline. We proposed that the reduction of SAI during RHI was due to the suppression of somatosensory tactile processing in S1, leading to its reduced inhibitory influence over M1. However, there was no significant reduction in SAI in the synchronous condition in the age-matched HC group in Study Two. This may be because different analyses were performed in Studies One and Two. The aim of Study One was to examine how the SAI was affected by RHI while Study Two was to compare the modulation of SAI by RHI in PD and controls. In Study One, participants who did not show SAI at baseline were excluded from the analysis while in Study Two, all patients and controls were analyzed regardless of the level of SAI at baseline.

No previous studies have examined the impact of vision or tactile stimulus on SAI. SAI under the influence of sensory inputs may be different from SAI at rest. In Study Two, we showed the overall reduction in SAI in PD-OFF. This suggests that SAI deficits in PD may occur under the influence of the sensory inputs rather than at rest.

5.4 Rubber Hand Illusion Effect on Long-latency Afferent Inhibition in PD Patients and HCs
In Study One, we showed that the long-latency inhibitory influence of somatosensory inputs was reduced after RHI. We speculated that the reduction of LAI reflects the involvement of cortical association areas such as PPC because we also showed the inhibitory PPC-M1 interaction was associated the strength of RHI. The cortical association areas may serve as a gate keeper to judge which somatosensory inputs should be weighted more when a conflict occurs among multisensory inputs. Study Two examined LAI modulation by RHI in PD patients. Again, it should be noted that we excluded the participants who did not showed LAI at baseline from the analysis in Study One whereas all the participants were included in the analysis in Study Two regardless of level of baseline LAI. Nevertheless, healthy participants in Studies One and Two showed the similar results.

In Study Two, PD-OFF patients showed reduced LAI at baseline compared to HC, and overall reduction in LAI compared to PD-ON. The results indicate impairment in tactile-motor integration in PD-OFF. It has been proposed that the somatosensory abnormalities in PD may be attributed to a change in the receptive fields of tactile inputs in the basal ganglia as a result of dopaminergic denervation in the striatum in PD (Conte et al., 2013; Suppa, Bologna, Conte, Berardelli, & Fabbrini, 2016). The tactile receptive field was proposed to be enlarged in PD and the enlarged receptive field may bring more “noise” into sensory perception resulting in increased tactile threshold. Dopaminergic medications were hypothesized to reduce both the noise and the threshold of tactile perception (Conte et al., 2013) and they can influence tactile perception at the basal ganglia level. Taking the theory into account, in PD-OFF, tactile stimulation from own hand during the RHI procedure might be contaminated by noises due to the enlarged receptive fields. The noisy tactile signal from own hand may have less influence on M1 in PD-OFF, resulting in reduced LAI.

On the other hand, in PD-ON, the noise level and the tactile threshold may be improved by dopaminergic medications leading to better tactile-motor integration represented as increased LAI. However, LAI was supposed to be decreased in the synchronous condition as seen in HC while it was increased LAI in PD-ON. Because the modulation of LAI only occurred in the synchronous condition, it is specific to the RHI experience.
As mentioned above, we suggested that the reduction of LAI in the synchronous condition in healthy individuals can be attributed to reduced somatosensory processing in cortical association areas. It is possible that the different modulation of LAI by RHI in HC and PD-ON is due to the altered activation pattern in cortical association areas, which was shown in several imaging studies in PD (Lozza et al., 2004; Ma et al., 2007; Moeller et al., 1999; Samuel et al., 1997). In PD, the weighting mechanism in cortical association areas may be defective. Because the abnormal LAI modulation by RHI was only seen in PD-ON but not in PD-OFF, dopaminergic medications may play a role in the LAI modulation. Dopamine receptors were predominantly found in striatal regions in the basal ganglia in monkey and human brain, followed by substantia nigra, thalamus and amygdala (Christian et al., 2009; Missale, Nash, Robinson, Jaber, & Caron, 1998). Dopamine receptors were also found in cerebral cortices such as frontal and temporal areas with lower amount than the basal ganglia (Rani & Kanungo, 2006). Because the amount of the dopaminergic receptors at the cortex was less than the basal ganglia, dopaminergic medications may not fully restore the altered function in the cortical association areas leading to no reduction in the influence of tactile inputs by the weighting system. In other words, the tactile-motor integration reflected as LAI may be increased in PD-ON because of the enlarged tactile receptor field and the improvement in tactile processing by dopaminergic medications at the basal ganglia level (Conte et al., 2013) and the PPC failed to suppress it during RHI.

### 5.5 PPC-M1 Interactions in PD patients and HCs

Both Studies One and Two showed that greater inhibitory PPC-M1 interaction was associated with stronger subjective feelings of RHI in HC. Study Two revealed that this association was not present in PD patients regardless of dopaminergic medication states.

Functional MRI studies in healthy individuals showed that the strength of RHI correlated with the level of activities in the PMv (Ehrsson et al., 2005; Ehrsson et al., 2004).
Increased activities in the IPL, the medial wall of intraparietal sulcus was reported during RHI (Ehrsson et al., 2004). As IPL is connected to PMv (Petrides & Pandya, 1984), IPL was assumed to be involved in the association between PMv activity and the subjective feeling of RHI. However, inhibitory rTMS to IPL did not disrupted the ownership feeling but instead, it led to attenuation of proprioceptive arm shift (Kammers, Verhagen, et al., 2009). Considering these previous studies, other areas in PPC may also be associated with RHI experiences. We focused on SPL in our study because this area involves static representation of hand (Jane E Aspell et al., 2012; Harris & Wolpert, 1998; Pellijeff et al., 2006) and the area is likely involved in multisensory integration during RHI.IPL involves visuo-motor integration and IPL-M1 interactions were modulated during motor tasks rather than when perceiving/ judging sensory stimuli. SPL receives greater tactile and proprioceptive inputs from S1 than IPL (Sakata et al., 1973) and converges them to create a body image relating to its location and posture relative to other body parts (Andersen, 1997; Gentile et al., 2011; Lewis et al., 2011). A TMS study showed that SPL-M1 interactions were facilitated compared to at rest while receiving vibratory stimuli to the index finger, indicating that SPL-M1 interactions was modulated by somatosensory inputs (Ziluk et al., 2010).All these studies suggest that SPL-M1 interaction may be modulated by RHI.

Area 5 in SPL was localized based on individual MRIs using anatomical landmarks in most participants. However, anatomical MRIs were not available for seven out of twenty-two participants in Study One, and four out of thirteen HC and three out of thirteen PD patients in Study Two. When the MRI was not available, the CP1 in the International 10-20 EEG system was used to locate SPL. This method may not be as accurate as using individualized MRI. However, a previous study showed that CP1 corresponded to SPL (Koessler et al., 2009) and therefore, SPL was likely stimulated in all the participants.

In Study One, SPL did not have significant influence over M1 at rest. Although the SPL-M1 interactions were not significantly different between at rest, in the synchronous and the asynchronous conditions, we found that the individual SPL-M1 interaction in the synchronous condition were associated with the strength of RHI experiences.
Participants who experienced stronger subjective feelings of RHI had greater inhibitory SPL-M1 interactions. The result suggests that SPL-M1 interaction is involved in RHI.

In Study Two, the correlation between the RHI strength and the PPC-M1 interaction in the synchronous condition was not observed in PD patients regardless of medication states, suggesting altered PPC-M1 interaction in response to RHI in PD. Only one study investigated PPC-M1 interactions in PD patient using the paired-pulse TMS technique and IPL was the stimulation target (Palomar et al., 2013). The IPL-M1 interaction was found to be facilitatory at 4 ms ISI at rest in HC while PD patients showed a lack of the IPL-M1 interaction. In our study, PD patients as well as HC showed no inhibitory or facilitatory influences of SPL on M1 at baseline. As SPL and IPL have different functions, the modulation of M1 by SPL can be different from IPL modulation. Our study showed that the SPL-M1 interaction at rest in PD patients did not differ from that in HC.

However, the lack of correlation between the strength of RHI experience and greater inhibitory SPL-M1 interactions in PD during RHI may indicate the altered SPL function in PD. Neuroimaging studies in PD suggested abnormal activations in PPC, including SPL (Lozza et al., 2004; Ma et al., 2007; Moeller et al., 1999; Samuel et al., 1997). In PD patients, SPL may not be involved in the occurrence of RHI because they still felt RHI to the similar extent with the HC in spite of the loss of correlation. PD patients may activate other cortical or subcortical areas than SPL to experience RHI. Association cortical areas, such as the premotor area, may compensate the SPL dysfunction to experience RHI because several studies have shown enhanced activation of this area in PD patients (Michely et al., 2015; Turner, Grafton, McIntosh, DeLong, & Hoffman, 2003). Cerebellum may play a role in the compensation because the local metabolism in this area is found to be increased in PD patients at rest (Ko, Lerner, & Eidelberg, 2015).

Alternative explanation of the lack of correlation in PD is abnormality in the white matter tracts which connect PPC to M1. Microstructural abnormalities were found in the superior longitudinal fasciculus (SLF) in PD (Burton, McKeith, Burn, Williams, & O'Brien, 2004; Gattellaro et al., 2009). As PPC projects to M1 directly or indirectly to M1 through SLF, the disrupted white matter could lead the aberrant PPC-M1 interactions in PD.
5.6 Converging Evidence for Disrupted Sensorimotor and Multisensory Integration in Parkinson’s disease

In summary, our study in PD patients showed the following results; 1) Normal RHI at the behavioural level in PD patients with ON and OFF dopaminergic medication status suggesting that visuo-tactile integration is preserved in PD, 2) Overall reduction in SAI in PD-OFF compared to controls, which was restored by dopaminergic medications, 3) Overall reduction in LAI in PD patients OFF medications compared to ON medications, 4) Increased LAI in PD patients with dopaminergic medications, with abnormal response to multisensory stimuli, 5) Disrupted PPC-M1 connectivity in PD-ON and OFF conditions.

These findings suggest that sensorimotor integration pathways in PD patients is disrupted at multiple levels. The overall reduction in SAI in PD-OFF suggests the disruption occurs at S1. The reduction of LAI in PD-OFF also suggests the disruption along the basal ganglia-thalamo-cortical pathway, likely involving both basal ganglia and cortical association areas. Functional interactions between PPC, one of the critical cortical areas for multisensory integration and M1, was altered in PD patients during multisensory integration suggesting deficits in the PPC-M1 pathway.

Functional MRI studies have shown that levodopa reduces the over-activated neural activity at rest in PD-OFF medication state as well as during visuo-motor tasks (Asanuma et al., 2006; Feigin et al., 2001; Ko et al., 2015; Ng, Palmer, Abugharbieh, & McKeown, 2010), suggesting a a “network normalization” effect of levodopa (Ko et al., 2015).” However, the effects of levodopa were prominent at rest rather than during motor tasks, indicating that the effects of levodopa is influenced by a task involved. Our studies employed a multisensory integration task which activated large areas of the sensory system. Dopaminergic treatment might have influenced these areas differently during our task from at rest or during other motor tasks. Our results suggest that the network involved in multisensory integration in the PD-OFF state was not restored by
dopaminergic treatment and that it was rather abnormally modulated. In the future, it will be interesting to test whether the network involved in multisensory integration will be restored by DBS therapy because cortical association areas receive inputs from basal ganglia.

5.7 Future Directions

5.7.1 Multisensory Integration in PD patients

Impairments in visuo-auditory integration and tactile-proprioceptive integration in PD patients have been reported in the past (Fearon et al., 2015; Konczak et al., 2008; Konczak et al., 2012; Li et al., 2010). In our study, visuo-tactile integration was tested in PD patients and was normal at the behavioural level. As vision and tactile perceptions are more involved in RHI than proprioception, RHI may not fully detect impairment of integration of proprioceptive inputs into other sensory inputs. In the future, a paradigm that evokes vision, tactile, and proprioception to the same degree may be used to further assess visuo-tactile-proprioceptive integration in PD.

Our behavioral result also suggests that visuo-tactile cue may be helpful for PD patients in rehabilitation settings. It is well known that auditory or visual cues often help PD patients with freezing of gait. As we showed that visuo-tactile integration is normal in PD patients, tactile cues combined with visual cues may be more effective than visual or auditory cue alone or visuo-tactile cue, which found to be less appreciated in the patients compared to HC (Fearon et al., 2015). The development of a method to facilitate visuo-tactile integration may have a potential role in rehabilitation in PD.

5.7.2 Disrupted and Compensatory Sensorimotor Integration Pathways in PD patients

108
Our neurophysiology studies found that sensorimotor integration pathways that normally evoked by RHI in HC were disrupted in PD patients. The disruption includes multiple brain areas such as S1 and PPC. Dopaminergic medications influence the pathways, suggesting the involvement of the basal-ganglia-thalamo-cortical circuits for sensorimotor integration. It will be intriguing to investigate how DBS modulates the abnormal sensorimotor integration during multisensory integration because a previous report showed that DBS restored LAI at rest (Wagle Shukla et al., 2013). Because visuo-tactile integration at the behavioural level is normal in PD, it is possible that other areas may be activated as a compensatory mechanism. In the future, it will be helpful to identify the areas that are abnormally activated in PD patients during visuo-tactile integration. Imaging techniques, such as functional MRI or magneto-encephalography (MEG), may help to identify the areas that are more activated in PD than controls during visuo-tactile integration. These neuroimaging and neurophysiological studies should be done with multisensory integration tasks rather than at rest as our findings suggested that the difference between PD and HC which found during the task performance may not be apparent at rest.

It is also possible that the functional connection between PPC and M1 was disrupted in PD rather than PPC dysfunction. In our study, we did not distinguish whether PPC itself was malfunctioning or the interactions between PPC and M1 was disrupted. MRI tractography of the SLF in PD maybe helpful to identify the nature of the disrupted PPC-M1 interactions.

5.7.3 The Influence of Dopaminergic Medications

Although dopaminergic medications did not influence multisensory integration at the behavioural level, they abnormally modulated the sensorimotor integration process which may involve association cortices at neurophysiological level. We did not observe any correlation between the neurophysiological results and the clinical scores, which mainly assessed PD motor signs. However, it is possible that the disruption of
sensorimotor integration by dopaminergic medications may be relevant to dyskinesias, which are excessive, involuntary movements induced by dopaminergic medications in advanced PD. Future study may examine the relationship between dyskinesias and the neurophysiological sensorimotor integration parameters.

5.7.4 Possible Intervention Therapy for PD patients

Our study explored neurophysiological modulation of sensorimotor integration pathways in response to multisensory stimuli. Multiple brain regions along the pathways seem to be disrupted in PD leading to an abnormal connection between the sensory and the motor systems in the brain. In the future, interventions restoring the connections between the two systems may improve symptoms in PD patients. One of the possible interventions would be inhibiting or facilitating cortical areas using non-invasive brain stimulation techniques such as repetitive TMS or transcranial direct current stimulation. PPC can be a target for the neuromodulation. However, whether it should be inhibited or facilitated needs to be further studied because imaging studies have shown conflicting results with reduced (Lozza et al., 2004; Ma et al., 2007; Moeller et al., 1999; Samuel et al., 1997) or over-activated (Wu et al., 2015) PPC at rest and over activation during a motor task (Catalan et al., 1999; Samuel et al., 1997; Tessa et al., 2010). In addition, further paired-pulse TMS study examining other areas such as premotor cortex or cerebellum should be performed to prove compensatory mechanisms in PD.

5.8 Conclusions

We conclude that multisensory integration evoked by RHI modulates both early and late stages of sensorimotor integration pathway. We show that multisensory integration occurs in PD patients at the behavioural level to the same extent as HC. Nevertheless, our neurophysiology results revealed alterations in the sensorimotor integration pathway mediating RHI, suggesting alteration of sensorimotor integration along the basal-
ganglia-thalamo-cortical pathway including S1, cortical association areas and the basal ganglia in PD.
References


