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Review

Aging and motor inhibition: A converging perspective provided by brain stimulation and imaging approaches

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ABSTRACT

The ability to inhibit actions, one of the hallmarks of human motor control, appears to decline with advancing age. Evidence for a link between changes in inhibitory functions and poor motor performance in healthy older adults has recently become available with transcranial magnetic stimulation (TMS). Overall, these studies indicate that the capacity to modulate intracortical (ICI) and interhemispheric (IHI) inhibition is preserved in high-performing older individuals. In contrast, older individuals exhibiting motor slowing and a declined ability to coordinate movement appear to show a reduced capability to modulate GABA-mediated inhibitory processes. As a decline in the integrity of the GABA-ergic inhibitory processes may emerge due to age-related loss of white and gray matter, a promising direction for future research would be to correlate individual differences in structural and/or functional integrity of principal brain networks with observed changes in inhibitory processes within cortico-cortical, interhemispheric, and/or corticospinal pathways. Finally, we underscore the possible links between reduced inhibitory functions and age-related changes in brain activation patterns.

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1. Introduction

1.1. Overview and aims

Normal aging is characterized by changes in the structural and functional integrity of the brain. These changes are marked, at the behavioral level, by progressive deterioration of motor and cognitive functions (Fling and Seidler, 2012a; Heuninckx et al., 2008; Langan et al., 2010; Nielson et al., 2002; O'Sullivan et al., 2001; see reviews, Seidler et al., 2010; Swinnen et al., 2011; Turner and Spreng, 2012). Some of the neurodegenerative processes in healthy aging, including changes in structural (e.g., Inano et al., 2011) and biochemical (e.g., Gao et al., 2013) properties of the brain, are argued to affect cortical inhibitory functions. Age-related deficits in the ability to control cerebral inhibition may explain many behavioral declines that healthy older adults experience in daily life, such as longer reaction times (e.g., Bedard et al., 2002; Jordan and Rabbitt, 1977), impaired coordination skills (e.g., Heuninckx et al., 2004; Serrien et al., 2000; Swinnen et al., 1998) and deterioration of fine motor functions (e.g., Calautti et al., 2001). There is also some evidence that inhibition at both corticospinal (Oliviero et al., 2006; Peinemann et al., 2001; Sale and Semmler, 2005) and spinal (Kido et al., 2004) levels of the central nervous system (CNS) decreases with advancing age. With the increasing use of neuroimaging techniques, a systems level approach has been developed which links age-related deteriorations in behavioral performance with changes in the functional and structural properties of brain networks that control motor inhibition (e.g., Coxon et al., 2009; Jackson et al., 2012).

At the cortical level, motor inhibition is largely mediated via activation of gamma-aminobutyric acid (GABA) receptors. GABA is a principal inhibitory neurotransmitter in the brain tissue of mammalians with a rich structural diversity of receptors and a dense representation of GABA-ergic interneurons in the neocortex (e.g., Blatow et al., 2005). Deficiencies or abnormalities in GABA-ergic activity have been documented in many cognitive and/or movement disorders, particularly in those diseases where excess or undesired movements emerge such as dystonia (Di Lazzaro et al., 2009) and epilepsy (Fedi et al., 2008) (see review, Hallett, 2011; Ramamoorthi and Lin, 2011). Importantly, the activity of cortical GABA-ergic inhibitory interneurons can be monitored in vivo with transcranial magnetic stimulation (TMS) (e.g., Siebner et al., 1998; Ziemann et al., 1996b; see review, Reis et al., 2008). This makes TMS a powerful tool to investigate the neurophysiological mechanisms associated with age-related changes in the regulation of GABA-ergic inhibitory function. The main aim of the present review is to provide, specifically, an overview of age-related changes in GABA-ergic mediated intracortical and interhemispheric inhibitory processes (as monitored with TMS), with particular reference to their impact on declines in motor performance with advancing age. A question of interest in this context is to what extent declines of GABA-ergic inhibitory functions are operating as underlying mechanisms for motor performance declines in the absence of overt pathology.

Functional neuroimaging techniques (e.g., functional magnetic resonance imaging, fMRI) and TMS are expected to generate complementary information on age-related changes in functional communication between brain regions: fMRI underscores the neuroanatomical boundaries of the brain regions involved in a task, whereas TMS is used to explore the presence and strength of inhibitory and excitatory projections between those brain regions and M1 more directly. Likewise, TMS and structural neuroimaging may be used to link age-related changes in the ability to modulate inhibition with differences in white matter microstructural organization and gray matter volume of brain regions that project into M1. Studies combining TMS and diffusion tensor imaging (DTI) in young adults have already indicated that inhibitory functions are strongly affected by differences in the brain's structural properties (Buch et al., 2010; Fling et al., 2011b; Neubert and Klein, 2010; Wahl et al., 2007). Similarly, there is also evidence to suggest that age differences in interhemispheric connectivity affect functional brain activity (Langan et al., 2010). In the past, TMS and neuroimaging techniques have been used to study aging independently from each other with some exceptions (Fling and Seidler, 2012a; Lanza et al., 2013; McGregor et al., 2013, 2011; Talelli et al., 2008a). The secondary aim of this review is, therefore, to further advance our current understanding of the mechanisms which underlie age-related changes in GABA-ergic inhibitory functions, associated with age-differences in motor performance, specifically focusing on findings from neuroimaging studies that reported age-differences in the brain's function (e.g., Heuninckx et al., 2008; Nielson et al., 2002) or structure (e.g., Coxon et al., 2009; O'Sullivan et al., 2001) that predict declines in motor functions.

1.2. Transcranial magnetic stimulation (TMS)

For the sake of clarity, here we provide a brief overview of the relevant TMS techniques which are central neurophysiological techniques in the current review. The physiological effect of TMS over the primary motor cortex (M1) can be quantified by measuring the motor-evoked potential (MEP) obtained from surface electromyographic (EMG) activity in the target muscles (Hallett, 2000; Rossini et al., 2010; Rothwell, 1997). The MEP amplitude obtained with TMS reflects the net effect of excitatory and inhibitory inputs to the motor cortex pyramidal cells. GABA-ergic inhibitory processes can be explored through the application of various TMS techniques. For example, the paired-pulse TMS paradigm (Kujirai et al., 1993), in which two separate pulses with a short (2–3 ms) interstimulus interval (ISI) are delivered to the motor cortex through the same TMS coil at rest, provides a measure for excitability of inhibitory interneurons within M1 (intracortical inhibition, ICI): the first sub-threshold (conditioning) stimulus is applied to recruit intracortical inhibitory interneurons which reduce the MEP amplitude produced by the second (supra-threshold) test stimulus. This phenomenon is referred to as short-interval intracortical inhibition (SICI). Evidence for the involvement of $GABA_A$-ergic inhibition in the generation of SICIs came from a pharmacological study by Ziemann et al. (1996a) which observed increased SICI by the ingestion of lorazepam, a positive modulator of the $GABA_A$ receptor. Another form of cortical inhibition induced with a paired-pulse TMS paradigm is long interval intracortical inhibition (LICI), in which two superthreshold stimuli of equal intensities applied with a long ISI (50–200 ms) (Valls-Sole et al., 1992). Evidence from a pharmacological study suggests that LICIs are mediated by $GABA_B$ receptors (Werhahn et al., 1999).

Paired-pulse paradigms that combine peripheral afferent nerve stimulation with TMS (e.g., Tokimura et al., 2000) may be used to monitor activity of non-GABA-ergic inhibitory pathways;

depending on the durations of ISIs between the conditioning (afferent, electrical) and test (TMS) stimuli. Inhibition induced by short ISIs (~20 ms), a phenomenon referred to as short latency afferent inhibition (SAI), is thought to involve cholinergic pathways (Di Lazzaro et al., 2000). For long latency afferent inhibition (LAI) (ISI ~ 40–70 ms), the inhibition of M1 appears to be mediated via GABA receptors rather than cholinergic ones (Sailer et al., 2002). Even though SAI and SICI appeared to be mediated by different mechanisms, evidence from a recent study showed that SAI can inhibit SICI and vice versa (Udupa et al., 2013). Importantly, both SICI and SAI appear to serve as significant predictors for age-differences in behavior (both motor and cognitive) among healthy individuals (e.g., Fujiyama et al., 2012a; Heise et al., 2013; Young-Bernier et al., 2012a).

The excitability of $GABA_B$-ergic interneurons in M1 can be explored by applying a single TMS pulse during the voluntary contraction of a target muscle. This produces a motor evoked potential (MEP) in the target muscle contralateral to the stimulated M1 followed by a period of suppressed EMG activity, which is termed contralateral silent period (cSP). The duration of cSPs has been reported to be prolonged by administration of $GABA_B$ agonist, baclofen (Siebner et al., 1998), suggesting that cSP could be mediated by $GABA_B$-ergic interneurons. Suppression of EMG activity in active muscles, ipsilateral to the stimulated hemisphere is termed ipsilateral silent period (iSP). Importantly, studies on subjects with callosal lesions have shown that iSPs can been taken to reflect recruitment of cortical inhibitory interneurons via transcallosal fibers passing through the posterior segments of the corpus callosum (e.g., Li et al., 2013; Meyer et al., 1995, 1998). The iSP is particularly well suited for investigating interhemispheric control of voluntary hand motor output (e.g., Giovannelli et al., 2009).

The status of interhemispheric inhibition (IHI) between different cortical brain regions and M1 on the contralateral hemisphere can be explored with a double-site TMS protocol (Chen et al., 2003; Ferbert et al., 1992; Lee et al., 2007; Ni et al., 2009; Talelli et al., 2008b). This technique combines the delivery of a conditioning-pulse over selected cortical sites prior to the test-pulse over M1 on the contralateral hemisphere. Typically, IHI is assessed at two ranges of ISI: short (8–10 ms) and long (40–60 ms), referred to as SIHI and LIHI, respectively. In general, SIHI is expected to be mediated through excitation of direct transcallosal inhibitory projections to the contralateral M1 whereas LIHI is likely to be mediated by indirect interhemispheric projections (e.g., Chen et al., 2003; Gerloff et al., 1998; Ni et al., 2009). Evidence from pharmacological studies suggests that LIHI may be mediated through activation of postsynaptic $GABA_B$ receptors since the administration of baclofen ($GABA_B$ agonist) significantly enhanced LIHI at ISIs between 20 and 50 ms (Irlbacher et al., 2007). The GABA-ergic mechanisms responsible for iSP and SIHI, however, are still unclear.

A number of studies have used these TMS techniques to investigate the involvement of inhibitory mechanisms in the regulation of voluntary movements in the general healthy population (e.g., Baldissera et al., 2002; Byblow et al., 2007; Coxon et al., 2006, 2007, 2009; Duque and Ivry, 2009; Duque et al., 2012, 2010; Hinder et al., 2010a; Perez and Cohen, 2008; Sinclair and Hammond, 2008, 2009; Tandonnet et al., 2010, 2011; van den Berg et al., 2011). However, only a limited number of studies have so far investigated the role of GABA-ergic inhibitory function in motor control in older adults. Evidence for a causal link between age-related differences in performance and the decreased ability to modulate inhibition has been provided lately through observations from an increasing number of TMS studies on healthy older adults (Davidson and Tremblay, 2013; Fling and Seidler, 2012a; Fujiyama et al., 2009, 2012a,b; Heise et al., 2013; Hinder et al., 2012; McGregor et al., 2011; Talelli et al., 2008a; Young-Bernier et al., 2012a; see Table 1 for details). The observations obtained in these studies are discussed in the present review.

2. Motor inhibition in aging: a general perspective

On a conceptual level, it has been argued that a degraded ability for inhibitory control is a primary cause of declined performance in cognitive (Burke, 1997; Hasher and Zacks, 1988; Kane et al., 1994; Kramer et al., 1994; Zacks et al., 2000) and motor tasks (Dustman et al., 1996, 1993). This hypothesis is based on the view that enhanced top-down control can improve performance in situations where performance is degraded by other factors. That is, to some extent, one can reduce performance decline by increasing attention to task-relevant stimuli or by inhibiting task-irrelevant information (Hasher et al., 1997). Top-down executive functions that organize inhibitory functioning, scheduling, planning, and task switching are cognitive functions most susceptible to the process of aging (Colcombe et al., 2005). Executive functions are believed to be largely subserved by the frontal lobes of the brain (West, 1996) (in interaction with cortical and subcortical structures), which are compromised by the aging process to a greater extent than other regions of the brain (Coxon et al., 2012; Raz, 2000; Resnick et al., 2003). fMRI studies also demonstrate additional brain activation in older adults (especially in frontal areas) when they are required to suppress irrelevant processing (e.g., Milham et al., 2002; Nielson et al., 2002). Using fMRI, Nielson et al. (2002), for example, investigated age-related changes in inhibitory control in a task requiring participants to respond to the letters 'X' and 'Y' when presented alternately, while consecutive presentations of same letters required no response. They found increased neural activity predominantly in right prefrontal and parietal regions and more extensive bilateral and prefrontal activity in older adults who successfully inhibited potentially erroneous responses to repeated target letters (e.g., X, X). The authors concluded that the additional activation in successful older adults was evidence of a compensatory mechanism to overcome declined inhibitory control. In contrast to cognitive tasks, the extent to which age-related changes in inhibitory functions contribute to motor performance declines in healthy aging is not well understood (Heuninckx et al., 2005).

The impact of aging on the balance between inhibition and facilitation has also been studied with TMS in healthy older individuals at rest (Bernard et al., 2013; Kossev et al., 2002; McGinley et al., 2010; Oliviero et al., 2006; Peinemann et al., 2001; Smith et al., 2009; Stevens-Lapsley et al., 2013; Wassermann, 2002). Trends, however, appear inconclusive with observations pointing towards either increased or reduced cortical inhibition. For example, Peinemann et al. (2001) reported that normal aging is associated with a decline of intracortical inhibition, as documented with paired-pulse TMS. Other studies reported no apparent impact of aging on intracortical (and/or interhemispheric) inhibition (e.g., Kossev et al., 2002; Stevens-Lapsley et al., 2013; Wassermann, 2002) or even an increased GABA-ergic mediated intracortical inhibition relative to younger adults under resting conditions (e.g., McGinley et al., 2010). Discrepancy between studies may be due to inconsistencies in the methodology, for example: exploring distal (Peinemann et al., 2001) vs. proximal (Kossev et al., 2002) hand muscles and/or age-and gender-differences in hormone levels (e.g., testosterone) which may affect the activity of $GABA_A$ receptors (Reddy and Jian, 2010; see review, Wang, 2011).

Declines in cerebral inhibitory processes during healthy aging, however, should not be attributed exclusively to reduced activity of GABA. For example, cortical GABA-ergic motor interneurons receive strong cholinergic innervation from afferent pathways through the thalamus (e.g., Nardone et al., 2012) whereas cortical regions contralateral to M1 may deliver synaptic input onto

Table 1
Key TMS studies which linked age-differences in cerebral inhibitory processes with behavioral changes in healthy aging. Information on age-differences in the brain's structure or function from neuroimaging data (fMRI or DTI) was provided in the main findings when available.

Study	Demographic characteristics[a]			TMS protocol[b]	Inhibitory neurotransmitter system(s)	Motor task	Main findings
Authors	Age group	No. of subjects	Age (years)				
Davidson and Tremblay (2013)	YA OL	13/4F 17/11F	22.4 ± 3.0 73.0 ± 7.6	iSP (right/left FDI)		Grooved pegboard Grip strength	Smaller iSP areas (lower transcallosal inhibition) predicted poorer performance on both manual tasks.
Fling and Seidler (2012a)	YA OA	16 15	18–28 65–76	iSP (right FDI)		Force production tasks: unimanual (right), bimanual simultaneous, bimanual independent	Better microstractuaral organization of the CC (estimated with DTI) predicted larger iSPs in YA but not in OA who showed the opposite trend. Superior inhibition was related to poorer bimanual performance in OA on all tasks.
Fujiyama et al. (2009)	YA OA	15/9F 15/9F	18–33 61–75	cSP (right ECR)	$GABA_B$	ISO and non-ISO movements with ipsilateral/contralateral hand and foot	cSP durations differed between contralateral and ipsilateral limb coordination in young but not in older adults.
Fujiyama et al. (2012a)	YA OA	15/8F 15/9F	18–29 58–84	as above	as above	as above	Sorter cSP duration (lower inhibition) was more prominent in older adults that showed lower coordination stability (Fig. 3).
Fujiyama et al. (2012b)	YA OA	13/10F 13/10F		SICI (right FDI)	$GABA_A$	Go/no-go pre-cued RT	SICIs did not differ significantly from baseline in older adults. Higher inhibition during movement preparation (250ms WS) predicted faster RTs (Fig. 1).
Heise et al. (2013)		64	20–88	SICI (right FDI)	$GABA_A$	SRT/CRT with right index finger (IF). Finger tapping (FT) with the right IF. 2FT task with right IF and little finger	Declining resting-state inhibition predicted poorer event-related modulation of SICI. Better event-related modulation of SICI predicted better performance on tasks demanding high-processing load (i.e., 2F tapping and CRT).
Hinder et al. (2012)	YA OA	13 13	22.2 ± 2.4 68.5± 2.9	SIHI/LIHI LM1→RM1 LPMd→RM1 (left FDI)	GABA-ergic, glutamatergic	SRT with right IF	For the older adults, modulation of LPMd-RM1 interactions early in the preparation period was associated with faster responses. Significant correlation between performance and LIHI (Fig. 2).
McGregor et al. (2011)	YA OA	12/5F 24/13F (active/ sedentary)	19–39 60–85	iSP (right FDI)		Manual performance with right IF, hand grip force, tapping speed, SRT	Longer iSPs and less positive fMRI BOLD signal of ipsilateral motor cortex in YA and active OA than in sedentary OA. For all groups, shorter iSP predicted increased BOLD on tapping.
Talelli et al. (2008a)		27	19–78	SIHI/LIHI LM1-RM1 (right FDI)	GABA-ergic, glutamatergic	Right hand grip to target forces between 15% and 55% MVC	Declined ability to modulate LIHI was correlated with increased fMRI BOLD signal at the non-active M1 (Fig. 4).
Young-Bernier et al. (2012a)	YA OA	24/14F 31/18F	22.5 ± 3.5 70.3 ± 3.8	SAI/LAI (right FDI)	GABA-ergic cholinergic	SRT with IF go/no-go with IF CRT with right/left IF dexterity pegboard test	SAI was significantly weaker in OA. Weaker SAI predicted poorer performance on CRT, go/no-go and dexterity. No age-differences in LAI.

[a] For all studies participants in all age groups were healthy volunteers with no known cognitive or motor disorders (unless mentioned otherwise). In Fujiyama et al. (2009), one subject in each age group was scored as a left handed. In Young-Bernier et al. (2012a), two YA and one OA were scored as left handed.

[b] Figure of eight coils (70–90 mm) were used in 10 of 12 studies. Hinder et al. (2012) used two 50 mm figure of eight coils for both test and conditioning pulses. Talleli et al. (2008a) used a 50 mm figure of eight coil for test stimulus (over RM1) and 70 mm figure of eight coil for conditioning stimulus (over LM1). YA = young adults, OA = older adults, F = female, FDI = first dorsal interosseous muscles, iSP = ipsilateral silent period, cSP = contralateral silent period, SICI = short intracortical inhibition, SIHI = short interhemispheric inhibition, LIHI = long interhemispheric inhibition, SAI = short afferent inhibition, LAI = long afferent inhibition, RM1 = right primary motor cortex, LM1 = left primary cortex, LPMd = left dorsal premotor cortex, ISO = isodirectional, NON-ISO = non-isodirectional, SRT = simple reaction time, CRT = choice reaction time, DTI = diffusion tensor imaging, fMRI = functional magnetic resonance imaging.

GABA-ergic motor neurons through glutamatergic circuits (e.g., Chen, 2004; Liuzzi et al., 2010; Perez and Cohen, 2008). There is evidence to suggest that declines in cholinergic activity (as evaluated with SAI) affect psychomotor speed and memory in normal cerebral aging (Young-Bernier et al., 2012a,b). Nevertheless, dysfunctions in activity of the aforementioned neurotransmitters mainly become visible in the presence of pathological aging. For example, the loss of motor inhibition has been documented with TMS in clinical conditions where movement disorders associated with aging emerge due to specific (pathology-related) changes in the brain's structural and/or biochemical properties, such as in Alzheimer's disease (Jackson et al., 2012; Pennisi et al., 2011) and Parkinson's disease (Cantello et al., 2007). While some of the mechanisms underlying pathological aging may overlap and/or explain reduced inhibitory processes in normal cerebral aging, their relationships to other biomarkers of healthy aging cannot be generalized.

Although age-related declines in motor inhibition may arise at various levels of the CNS, the present review focuses specifically on the effect of normal cerebral aging on cortical inhibitory processes. Principal regions of interest in this respect are the prefrontal/premotor–motor networks (e.g., Byblow et al., 2007; Duque et al., 2012) and the fronto-basal-ganglia network (Aron et al., 2007; Aron and Poldrack, 2006; Coxon et al., 2012). Generally, the cortical regions and intrahemispheric neuronal pathways that set up the aforementioned networks are good candidates for exploring the aging motor system since they are involved in the regulation of inhibitory processes during daily life situations where overt suppression of responses is required, such as go/no-go or go/stop reactions. Other regions of interest are the transcallosal pathways which account for interhemispheric inhibitory processes between the two M1s, as well as between the M1s and prefrontal/premotor regions in the contralateral hemisphere (Baldissera et al., 2002; Byblow et al., 2007; Fujiyama et al., 2012a; Ni et al., 2009; Perez and Cohen, 2008; Talelli et al., 2008b; van den Berg et al., 2011). As such, we consider inhibitory functions within the key motor area (i.e., M1) as well as projections from other cortical regions to M1. Regarding the behavioral (motor) aspects of aging, slowing of reaction times (e.g., Cuypers et al., 2012; Fujiyama et al., 2012b, 2013, 2011; Hunter et al., 2001; Morgan et al., 1994; Salthouse, 1991, 1996) and decreased ability to coordinate movements with the upper and/or lower limbs (e.g., Fujiyama et al., 2009, 2012a; Goble et al., 2010; Heuninckx et al., 2004; Serrien et al., 2000; Van Impe et al., 2009) have been documented as typical markers of performance decline in healthy older individuals due to loss of inhibition.

3. Neurophysiological basis of age-related changes in inhibitory control: evidence from TMS studies in healthy older adults

3.1. Age-related changes in inhibitory control involved in the preparation and generation of speeded motor responses

Aging is associated with progressive slowing of reaction times (Jordan and Rabbitt, 1977; Salthouse, 2000). Many behavioral studies suggest that aging affects the readiness of the motor system, particularly in choice reaction time tasks (Adam et al., 1998; Bherer and Belleville, 2004; Jordan and Rabbitt, 1977; Proctor et al., 2005; Salthouse, 2000). Previously, this slowing has been attributed to age-related declines in central processing (Clarkson, 1978; Crossley and Hiscock, 1992; Jordan and Rabbitt, 1977; Walsh, 1976) and working memory (Briggs et al., 1999). Observations from electroencephalography (EEG) studies confirmed that behavioral slowing may be due to changes in response generation, rather than in stimulus processing and sensorimotor integration stages (Falkenstein et al., 2006; Roggeveen et al., 2007; Yordanova et al., 2004). Furthermore, some studies also found age-related differences in the preparatory period (i.e., prior to an imperative signal). For example, age-related changes in preparatory state have been indexed in EEG studies by cortical slow potentials, with older adults showing increased amplitudes of the stimulus-preceding negativity and attenuated contingent negative variation (CNV) amplitudes in response to a warning signal (Hillman et al., 2002). Sterr and Dean (2008) similarly observed attenuated CNV amplitudes in older adults during the waiting period (foreperiod) for the imperative signal during execution of a motor task, suggesting that neural processing in older adults was less efficient relative to younger adults in the preparatory period, perhaps reflecting deterioration in attentional processes. Interestingly, TMS studies with younger participants showed that faster reaction times were associated with a release of intracortical inhibition during the foreperiod, indicating that decreased cortical inhibition may be an important component of the preparation process prior to response initiation (Sinclair and Hammond, 2008, 2009). Thus, inhibitory processes required for response preparation are likely linked to GABA-ergic inhibitory functions.

Overall, evidence from these studies suggests that response preparation involves concurrent activation of two functionally opposing mechanisms which are instrumental for the shortening of reaction times: (1) suppression of corticospinal excitability by increasing cortical inhibition, prior to the onset of the imperative signal (impulse control) and (2) release of cortical inhibition prior to the generation of motor output. As preparation is generally thought to reflect an activation process through an increase of cortical excitability, the suppression of corticospinal excitability during movement preparation (i.e., the time elapsing between the warning signal and the imperative signal) may, on the one hand, appear surprising. On the other hand, temporal preparation during pre-cued choice or go/no-go reaction time paradigms entails suppression of potential premature and/or preferred responses during the waiting period (Davranche et al., 2007; Duque and Ivry, 2009; Hasbroucq et al., 1997) to secure a correct response. This suppression is expected to be followed by a rapid, selective facilitation of corticospinal excitability in the target muscles through release of SICI after the onset of the imperative stimulus (Duque et al., 2010; Tandonnet et al., 2010). In contrast, the reduction of corticospinal excitability observed after a no-go signal is hypothesized to reflect the operation of an inhibitory mechanism related to selectively withholding a response (Tandonnet et al., 2011). Questions of interest that remain, however, are how and to what extent age-related changes in the balance between inhibitory and excitatory processes affect reaction time performance in normal aging. In the following, we will examine the effect of aging on intracortical and interhemispheric inhibitory processes during response preparation.

3.1.1. Intracortical inhibition

Evidence to directly link decreased ability to modulate corticospinal excitability in general and intracortical inhibition in particular with motor slowing in healthy older adults has been provided in recent TMS studies (Fujiyama et al., 2012b, 2011; Heise et al., 2013; Young-Bernier et al., 2012a). Specifically, in Fujiyama et al. (2012b), age-related changes in the time course of corticospinal excitability and intracortical inhibition during a warned reaction time task were investigated by delivering TMS during preparatory (time between warning and imperative signal) and response generation (after the onset of imperative signal) periods (Fig. 1A). Age-related differences in the time course of MEP suppression during the preparatory interval, when inhibition related to impulse control operates (Davranche et al., 2007; Duque and Ivry, 2009; Touge et al., 1998), were characterized by smaller modulations of corticospinal excitability in older individuals relative

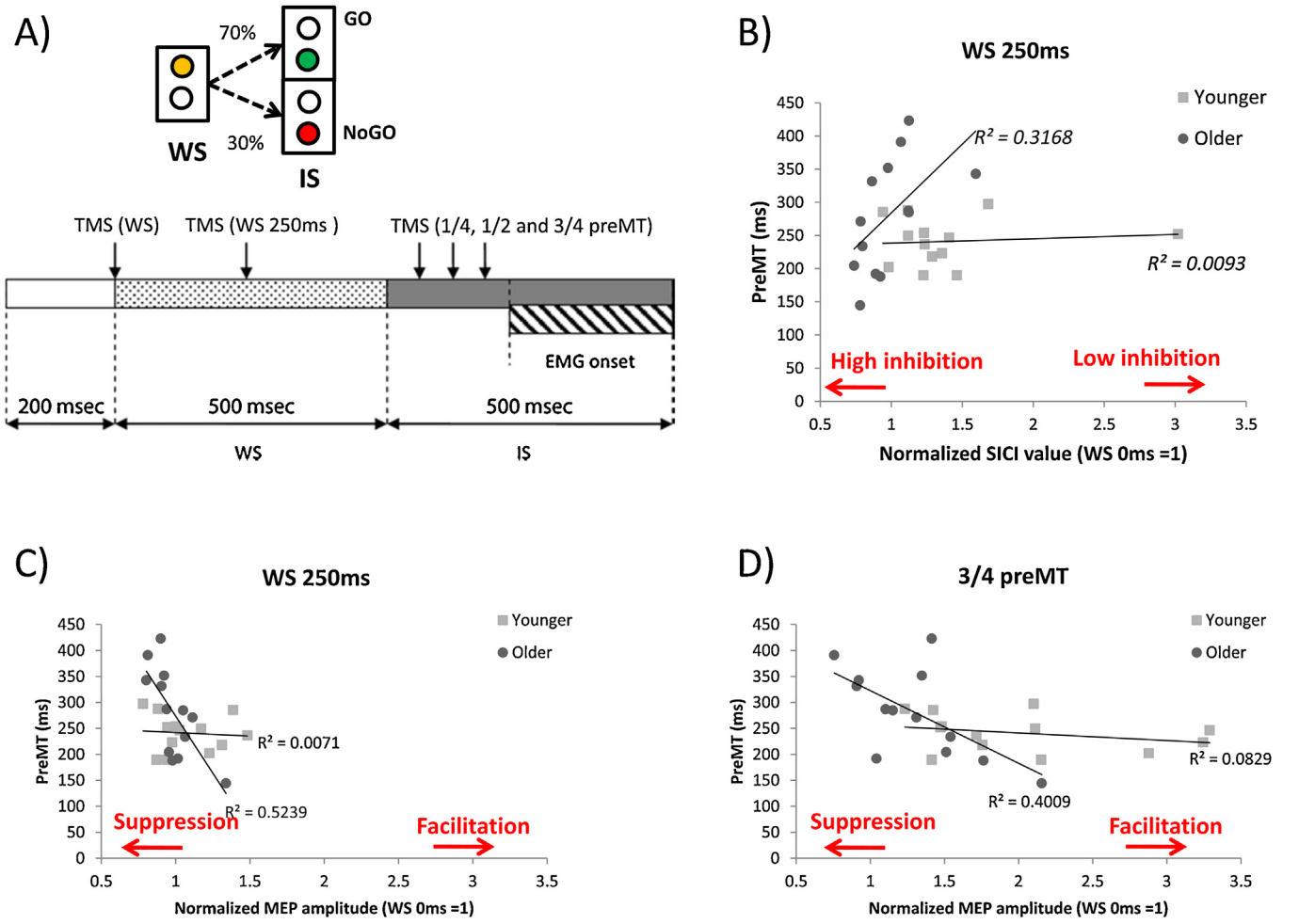

Fig. 1. Excitatory and inhibitory processes associated with psychomotor slowing. (A) The go/no-go task and TMS protocol used in the study of Fujiyama et al. (2012b). A warning signal (WS) was followed by an imperative signal (IS) to which participants were required to respond with a rapid flexion of the right thumb (go condition) or withhold their response (no-go condition). Single- and paired-pulse TMS were administered at various times between WS and IS (response preparation phase) and between IS and onset of response-related muscle activity (response generation phase) in the right thumb. (B) Correlations between premotor time (preMT) and normalized SICI obtained at WS 250 ms (circles are data from older adults and squares are data from younger adults). A significant positive correlation ($p < 0.05$) between preMT (ordinate) and normalized SICI (abscissa) was observed in older but not in younger adults. Significant negative correlations between preMT (ordinate) and normalized MEP amplitude (abscissa) in older adults were observed at WS 250 ms (C) and 3/4 preMT (D). preMT = The latency between the onset of the IS and the first occurrence of the onset of response-related EMG activity. All illustrations were reproduced from Fujiyama et al. (2012b) with permission.

to that observed in younger adults. Although there was no age-difference in the ability to modulate intracortical inhibition at the group level, a greater recruitment of $GABA_A$-ergic mediated intracortical inhibition (i.e., smaller SICI values) during the preparatory period was associated with faster RTs in older but not in younger adults (Fig. 1B). During the preparatory period, simultaneous activations of excitatory and inhibitory circuits appear instrumental in the generation of fast responses (Fig. 1C and D), with the processes of preparing to dispatch the motor command (MEP facilitation) and impulse control (increased ICI) occurring at the same time. In contrast, for the motor generation stage, a rapid increase of net corticospinal excitability, to which a release of ICI partly contributes, results in fast responses. Interestingly, observations from a recent study by Heise et al. (2013) showed a declined ability to modulate the $GABA_A$ activity as a function of age; specifically, event-related modulation of $GABA_A$-ergic inhibition in terms of a release of inhibition was drastically reduced in subjects of older age. A question of importance, in this respect, is whether age-related changes in resting-state inhibition would be directly related to declines in the ability to modulate inhibition. Evidence from the same study of Heise et al. (2013) appears to verify this link by showing that resting-state inhibition is a significant predictor for a decline in task-related modulation of inhibition, suggesting that lower resting-state inhibition is associated with degraded task-related inhibitory control in older adults (Heise et al., 2013).

Another question of importance is whether age-differences in the generation of speeded motor responses are associated with altered activity of neurotransmitter systems which are not GABA-ergic. Evidently, motor slowing is attributed in part to a decreased ability to modulate cholinergic activity. Importantly, observations from a recent study of Young-Bernier et al. (2012a) showed that SAI, a phenomenon linked with dysfunction of cholinergic activity in M1 (e.g., Di Lazzaro et al., 2000; Nardone et al., 2012), is selectively reduced in healthy older individuals. Also, there is some consensus that psychomotor slowing in healthy older adults is not caused exclusively by reduction in the activity of $GABA_A$-ergic motor interneurons. For example, Young-Bernier et al. (2012a) showed that SAI levels were significant predictors for performance in a dexterity task (explaining 32% of the variance), choice reaction time (17%), and go/no-go reaction time (10%). While evidence from this study suggests that declines in cholinergic processes may explain age-related decline in regulation of intracortical inhibition in M1, the two inhibitory mechanisms are possibly coupled with each other (Udupa et al., 2013). Future studies are warranted

to consider association between these two inhibitory mechanisms investigating SAI and SICI in older adults.

Finally, a growing body of literature shows that response preparation is controlled by inhibitory projections from non-motor areas and secondary motor areas to M1. For example, Duque et al. (2012) found that transient disruption of the dorsal premotor cortex (PMd) by repetitive TMS (rTMS) increased the excitability of contralateral M1. Direct evidence for the involvement of prefrontal and premotor areas in movement preparation has also been demonstrated with EEG (Huster et al., 2013; Wheaton et al., 2008) and fMRI (Duann et al., 2009; Smith et al., 2013; Watanabe et al., 2002). In particular, a network consisting of bilateral premotor area, anterior cingulate cortex and supplementary motor area (SMA) was highly implicated in the preparation of a motor response when movements were precued (Smith et al., 2013; Watanabe et al., 2002). Based on these findings, we propose that the reduced ability to modulate inhibition in healthy older adults could originate at the interface between prefrontal/premotor regions and M1 rather than within M1 per se. In particular, age-related differences in inhibitory (or excitatory) projections from the dorsolateral prefrontal cortex (DLPFC), inferior frontal cortex (IFC), and PMd to M1 should be considered in this respect.

3.1.2. Interhemispheric inhibition

During preparation and execution of an action, IHI from the passive to active motor cortex is reduced to allow the planned action, while IHI onto the non-responding cortex is increased to prevent unwanted mirror activity (Duque et al., 2007; Hinder et al., 2010b). This predicts that task-related modulation of IHI plays a functional role in the preparation and generation of speeded motor responses. Interhemispheric interactions are hypothesized to be particularly important during movement preparation given that 'preparatory neurons' are more abundant in premotor, compared to primary motor regions during a choice reaction time task (Riehle and Requin, 1989). In particular, the left PMd assumes a dominant role in the preparation of movements of either hand, when movements occur in response to external cues (Cisek et al., 2003; Crammond and Kalaska, 1996; Duque et al., 2012; Schluter et al., 1998). Accordingly, any changes in interhemispheric interactions emanating from motor/premotor areas that occur with advancing age would assume significance for control of movement preparation and movement initiation. Indeed, Hinder et al. (2012) reported greater task-related facilitatory changes in the nature of the interactions between left PMd and right M1 for older, compared to young adults, during response preparation in a simple reaction time task using the left hand (Fig. 2). Young and older adults exhibited a similar degree of inhibition from left to right M1 at rest. The task-related M1–M1 IHI modulations, however, were not correlated to reaction time performance. In contrast, the ability to modulate left PMd-right M1 IHIs early in the preparation period was associated with faster responses, suggesting that specifically timed modulation of these pathways may be a compensatory mechanism to overcome, at least in part, slowing of motor responses in the older adults group. Interestingly, the aforementioned effect was more prominent for LIHI than SIHI, suggesting that tuning of M1 excitability during response preparation in the older adults also involves indirect pathways from left PMd to the right M1.

Finally, recent findings from Fujiyama et al. (2013) showed that, particularly for older adults, M1 ipsilateral to the responding hand also assumed a functional role during movement preparation. Specifically, the authors showed that transient disruption of the left M1 function with double-pulse TMS during response preparation for speeded motor responses with the left index finger resulted in delayed response time in older but not younger adults. This finding is consistent with the view that the bilateral activation of M1 in older adults during unimanual actions is functional and may help to compensate for motor slowing that occurs with advancing age. The fact that, in older adults, preparing for movement with one limb entails activation of a bilateral cortical network could partly explain the early findings of Levin et al. (2011), showing that the older adults differentially tuned excitability of the active and non-active M1s during the preparatory period in a simple reaction time. Specifically, these authors reported that older adults tended to increase readiness of the moving side to the upcoming go-signal during a simple reaction time by increasing the excitability of corticospinal projections to the active hand while suppressing the descending tracts of the resting hand. The authors suggested that this earlier "differential facilitation" of the corticospinal pathways was a manifestation of an optimized preparatory strategy that may be beneficial for overcoming motor slowing. Based on the observations from Hinder et al. (2012), one would expect that the differential tuning of corticospinal excitability during performance of a simple reaction time task (as reported by Levin et al., 2011), is mediated (in part) by the modulation of interhemispheric interaction between premotor and primary motor regions. More specifically, the release of IHI from premotor regions to the M1 contralateral to the moving side resulted in the earlier facilitation of MEP amplitude, while increasing IHI from the same premotor regions to M1 contralateral to the resting hand was reflected in the suppression of MEPs in the non-moving hand.

3.2. Age-related differences in inhibitory processes during interlimb coordination

Previous studies investigating coordination of the upper and/or lower limbs in healthy older adults have shown that their ability to coordinate movements declines with age (e.g., Goble et al., 2010; Greene and Williams, 1996; Heuninckx et al., 2004; Serrien et al., 2000). This is particularly evident, for example, during conditions where suppression of preferred movement patterns is required, such as in coordination behaviors that require moving two or more joints/limbs at different amplitudes, directions and/or speeds (e.g., Levin et al., 2004b; Serrien and Swinnen, 1997; Swinnen et al., 2001). Generally, when performing the same coordination task, older adults will normally show higher movement variability, larger phase wandering, and more frequent phase transitions relative to those seen in younger individuals (Heuninckx et al., 2004; Lee et al., 2002; Serrien et al., 2000; Temprado et al., 2010; Wishart et al., 2000). These markers of deteriorated performance tend to emerge at higher movement speeds whereas older adults might still be able to achieve comparable levels of performance with their younger counterparts at comfortable speeds (e.g., Heuninckx et al., 2004; Temprado et al., 2010; Wishart et al., 2000). The aforementioned findings may suggest, at first, that the age-related deterioration of coordination might be a consequence of decreased central sensory processing and sensorimotor integration (e.g., Heuninckx et al., 2004, 2005). However, as it is necessary to inhibit conflicting neural outputs that tend to promote preferred coordination patterns in order to successfully perform the non-preferred coordination pattern, impaired inhibitory control is also expected to cause deficits in coordinated movements in older adults. In this section, we will outline age-related differences in coordination performance that may be associated with declines in the ability of older adults to modulate cortical inhibition.

The manifestation of inhibition in interlimb coordination has been explored with TMS (e.g., Baldissera et al., 2002; Byblow et al., 2007; Carson and Kelso, 2004; Levin et al., 2004a; van den Berg et al., 2010). Generally, these studies revealed that cyclical activation of upper or lower limb muscles can result in a phasic modulation of the excitability of the contralateral homologous or ipsilateral motor pathways. For example, Byblow et al. (2007) showed that SICIs obtained from a resting forearm extensor muscle were selectively

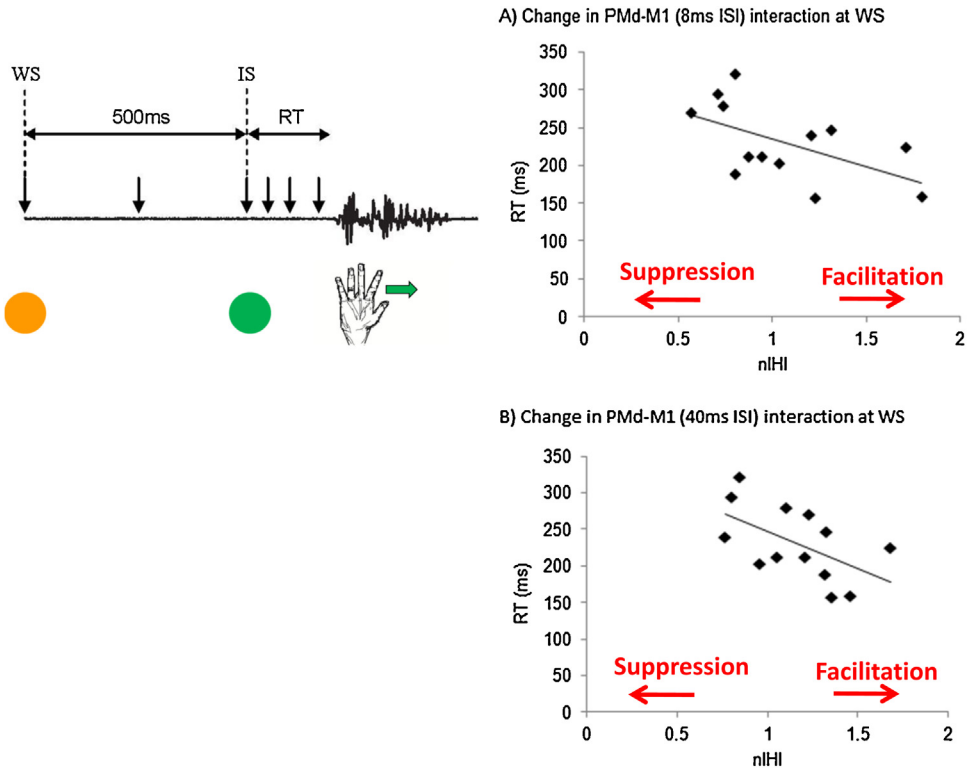

Fig. 2. Interhemispheric interactions and psychomotor slowing. Association between the neurophysiological predictors for interhemispheric inhibition (SIHI and LIHI) and performance measures (i.e., reaction time). Higher facilitation, probably by release of inhibition, early in preparation (coincident with warning signal = WS) was associated with faster responses for both 8 and 40 ms. Task and TMS protocol: a warning signal (orange light, WS, here represented by the white circle) was presented for 500 ms followed by the green imperative ('go') signal (imperative signal = IS), represented by the gray circle. Participants responded to the IS as quickly as possible by rapidly abducting their left index finger in the horizontal plane. TMS was delivered at six time points as indicated by the vertical arrows. Illustrations were reproduced from Hinder et al. (2012) with permission.

reduced during dorsiflexion compared to plantarflexion movement of the ipsilateral lower limb, suggesting that intracortical inhibition was reduced to promote the isodirectional coordination pattern. A similar reduction of ICI in hand muscles from both discrete and phasic dorsiflexion movements of the ipsilateral foot was reported using the silent period TMS protocol (Sohn et al., 2005; Tazoe et al., 2007). Specifically, Sohn et al. (2005) found that cSP duration from a hand muscle was reduced (i.e., decreased inhibition) when TMS was triggered by foot movement compared to without foot movement, indicating that cortical inhibition on the hand was released when the task required moving another part of the body. However, until recently, there has been limited research using TMS to investigate the role of inhibitory processes in the control of interlimb coordination performance in aging. A question of importance, therefore, is the extent to which the greater difficulty observed in the performance of interlimb movements by older adults is a consequence of reduced ICI and IHI inhibitory processes in aged participants.

3.2.1. *Intracortical inhibition*

The first evidence for linking lower coordination stability with declined ability to modulate ICI in older adults was provided by Fujiyama et al. (2009). Specifically, they assessed cSP duration in the right extensor carpi radialis (ECR) muscle during performance of cyclical hand–foot movements with contralateral and ipsilateral limb combinations that moved in the same or opposite directions (Fig. 3A). Results revealed that older as compared to young adults showed lower levels of inhibition (shorter cSPs) in the tasks involving ipsilateral movements (i.e., moving hand and foot on the same body side). A significant finding in this respect is the fact that task-related modulations of cSP durations, which are mediated by activity of $GABA_B$ receptors (e.g., Siebner et al., 1998), were observed in younger but not older individuals. Specifically, younger adults displayed significantly longer cSP durations (i.e., an increase of $GABA_B$ activity) in the most difficult condition (i.e., movements with the lowest coordination stability) which was the non-isodirectional pattern with ipsilateral limbs (mean cSP = 148 ms) in comparison to baseline phasic hand movement or contralateral (iso/non-isodirectional hand–foot coordination; all cSPs < 134 ms). In contrast, no significant difference in cSP was observed in the older adults across all task coordination modes (cSP ranged between 137 and 140 ms). The subsequent studies by Fujiyama et al. (2012a) provided further evidence for the link between behavioral declines and inhibitory processes in the aging brain. In their first experiment, using the similar TMS protocol and task (Fig. 3B), the authors compared excitatory and inhibitory processes in high and low performing older adults. As in the study of Fujiyama et al. (2009), younger adults exhibited longer cSP (i.e., an increase of $GABA_B$ activity) with ipsilateral limb combinations than contralateral limb combinations (Fig. 3C). Indeed, coordination stability metrics (performance) and cSP duration metrics in the older adults group covaried with each other, showing that longer cSPs (i.e., an increase of $GABA_B$ activity) were associated with improved performance (Fig. 3D). Further inspection of the results revealed that older adults with the lowest behavioral performance exhibited significantly shorter cSP duration than older adults with significantly more stable performance (i.e., higher performers). These findings proposed for the first time a causal link between age-related differences in the ability of older adults to activate $GABA_B$-ergic circuits and their ability to perform an interlimb coordination task. The difference between high and lower performers is consistent with the hypothesis that ICI plays a prominent

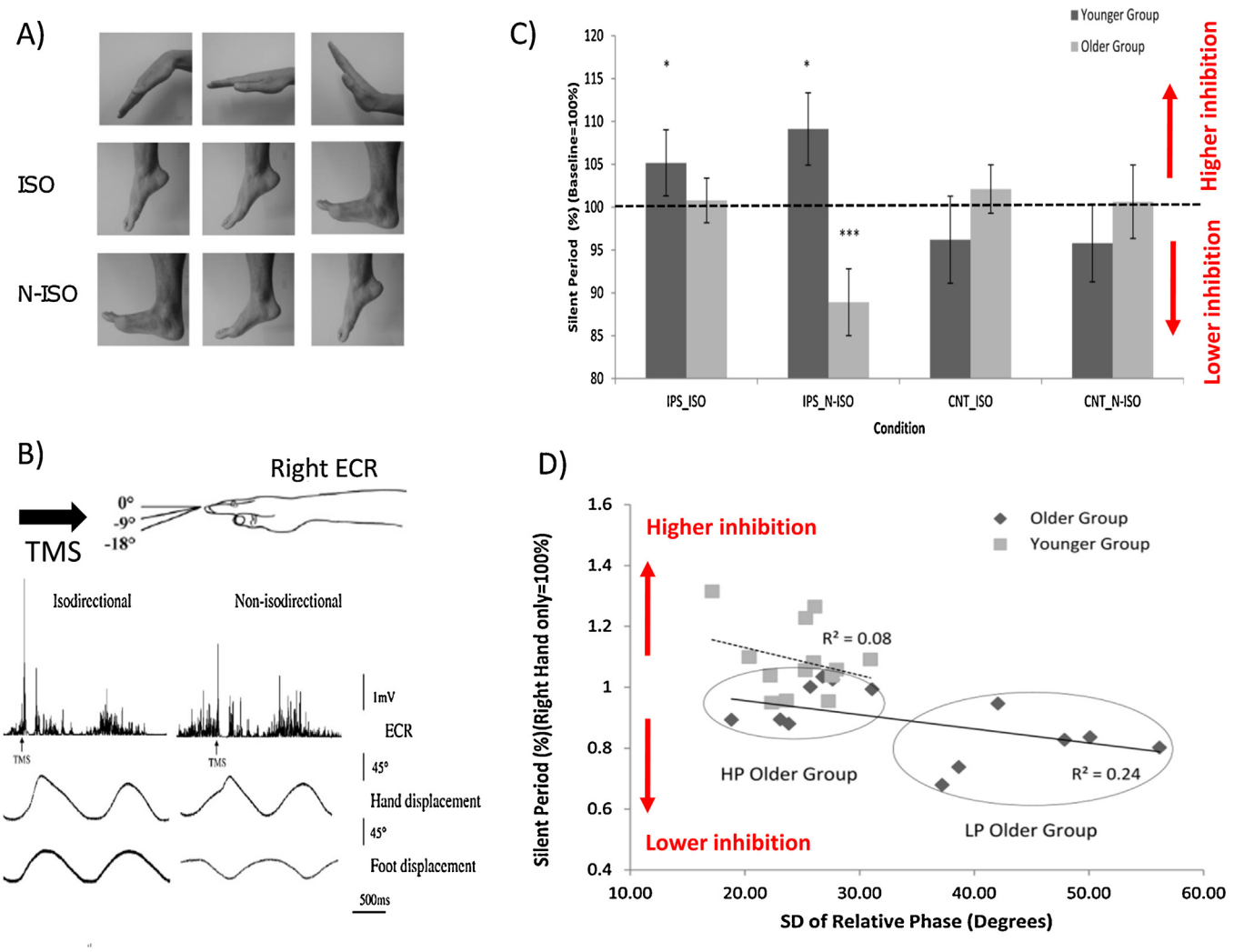

Fig. 3. Intracortical inhibitory processes and interlimb coordination. The TMS protocol and the behavioral coordination tasks were used in experiment 1 of Fujiyama et al. (2012a). (A) Cyclical coordination of the hand and foot according to the isodirectional mode (ISO; both limb segments are moved in the same direction) and the nonisodirectional mode (N-ISO; both segments are moved in opposite directions). (B) Magnetic stimulation (TMS) was delivered at 3 right hand positions (−18°, −9°, 0°, relative to horizontal) eliciting right extensor carpi radialis (ECR) muscle stimulating left M1. (C) Histograms showing the mean right extensor carpi radialis (ECR) silent period (SP) duration relative to the baseline (hand only) for the younger and older group (dashed line). Error bars indicate 95% confidence intervals. Asterisks indicate statistically significant differences between conditions in each group (*$p < 0.05$; ***$p < 0.001$). *Abbreviations*: CNT_ISO, contralateral isodirectional; CNT_N-ISO, contralateral non-isodirectional; IPS_ISO, ipsilateral isodirectional; IPS_N-ISO, ipsilateral non-isodirectional. (D) Mean standard deviation of relative phase (SD of RP) and mean right ECR silent period duration relative to the baseline (hand only) for lower (LP) and higher performing (HP) groups in younger and older groups in experiment 1. Illustrations were reproduced from Fujiyama et al. (2012a) with permission.

role in permitting successful execution of the more difficult interlimb coordination patterns that require suppression of the more inherently stable modes (Classen et al., 1998; Garry et al., 2004).

3.2.2. Interhemispheric inhibition

The second part of Fujiyama's study (Fujiyama et al., 2012a, Experiment 2) examined the primary motor cortex ipsilateral to the moving hand by measuring MEP amplitude and cSP duration from the left ECR during performance of ipsilateral (right hand and foot) and heterolateral (right hand and left foot) coordination tasks. Consistent with previous studies (Hinder et al., 2010a; Sohn et al., 2003), both younger and older adults showed shortened cSP durations (i.e., a decrease of $GABA_B$ activity) in the tonically contracted left ECR when the right hand was moving relative to the baseline condition in which only the left hand was tonically contracted (albeit this effect was more pronounced in young adults). The decreased cSP durations during the right hand movement were accompanied by a significant increase of MEPs measured from the left ECR (only in young adults). The authors proposed that phasic activation of the muscles on one side can increase excitability of the contralateral homologous motor pathway (e.g., Carson et al., 2004). As in the previous studies (Fujiyama et al., 2009, 2012a, Experiment 1), younger adults showed significantly longer cSP durations (i.e., an increase of $GABA_B$ activity) during performance of the ipsilateral non-isodirectional movements than in the other movement conditions which did not differ from each other. This effect was not seen in the older adults. The aforementioned finding suggests that, in younger adults, corticospinal inhibition in both hemispheres was higher during the performance of ipsilateral non-isodirectional limb combinations compared with the other coordination modes. The authors then proposed that modulation of the intracortical inhibitory pathways in the ipsilateral M1 is linked to the modulation of cSP durations within the contralateral M1, possibly through interhemispheric inhibitory pathways (Hinder et al., 2010a,b). Older adults, in contrast, showed no modulation of cSP durations in the left ECR across conditions, suggesting that the ability to regulate $GABA_B$ activity through the transcallosal pathways declines with aging.

Further evidence for linking declined coordination ability in older adults with regulation of transcallosal inhibition was provided in a study of Fling and Seidler (2012a). Specifically, these authors looked into modulations of iSPs in the first dorsal interosseous (FDI) muscle of the dominant (right) hand during performance of three force production tasks including: (1) unimanual (right hand) constant force, (2) bimanual constant force (bimanual simultaneous), and (3) right hand constant force and left hand sine wave tracking force (bimanual independent). Observations from this study revealed a trend for stronger transcallosal inhibition in young adults, but no age group differences were noted. These findings are in contrast to observations from other studies where transcallosal inhibition (assessed with the same method) was strongly influenced by age (e.g., Davidson and Tremblay, 2013; McGregor et al., 2013, 2011). Interestingly, Fling and Seidler (2012a) reported that higher transcallosal inhibition (i.e., longer and larger iSPs) was significantly correlated with poorer performance of the bimanual independent task (assessed by dominant hand force variability) in both age groups. This observation contrasts with findings from other studies on aging (e.g., Fujiyama et al., 2012a,b; Heise et al., 2013) where higher levels of inhibition (both ICI and IHI) in older adults were found in better performers. Although conflicting, the findings reported by Fling and Seidler (2012a) provided some vital evidence about how interhemispheric communication may adapt with aging. Importantly, Fling and Seidler (2012a) found that: (1) higher transcallosal inhibition was related to poorer performance in older adults across all tasks, whereas in young adults higher transcallosal inhibition predicted poorer performance only during the bimanual independent task and (2) higher transcallosal inhibition predicted lower interhemispheric facilitation (assessed by MEP amplitudes in the left FDI during unimanual force production) in younger individuals but not in older adults. Interestingly, a second study of the same authors (Fling and Seidler, 2012b) which involved only younger adults (but with the same TMS protocol and tasks) has shown that increased transcallosal inhibition reduced motor overflow during unimanual force production but limited performance during performance of independent bimanual force production. Taken together, observations from Fling and Seidler (2012b) suggest that while some degree of inhibition is required for independent bimanual control, the ability to suppress transcallosal inhibition is also essential since the degree of cooperation between the two hemispheres is expected to vary across different tasks.

Further evidence for task-related reduction in interhemispheric inhibition with advancing age has been provided by Talelli et al. (2008a,b). In the first study (Talelli et al., 2008b), TMS was used to assess age-related differences in interhemispheric balance between the two M1s, monitoring SIHIs (ISI = 10 ms) and LIHIs (ISI = 40 ms) from left to right M1 at rest (rest-IHI) and during isometric activation of the right hand (active-IHI). Task-related changes in IHI were then expressed as the ratio of the values of the active IHI relative to IHI at rest (with values < 1 reflecting stronger inhibition, and values > 1 reflecting less inhibition). They showed an overall tendency for stronger SIHI and LIHIs from left to right M1 during activation of the right index finger muscle relative to rest. However, age-related reduction in the extra inhibition imposed by the activation of right index finger muscle was seen only for LIHIs (Fig. 4A, left hand panel). Based on this observation the authors suggested that the amount of inhibition targeting the ipsilateral (right) motor cortex increased when the right hand was activated but this effect was *"gradually attenuated and often reversed with increasing age"* (c.f. Talelli et al., 2008b). In the subsequent study by Talelli et al. (2008a), fMRI and TMS were combined to map task-related changes in interhemispheric inhibition onto task-related activation changes in motor-related brain areas during the performance of a similar behavioural task. The authors observed that activity in the ipsilateral M1 during the active motor task was greater in subjects that showed lower LIHIs from left to right M1 (Fig. 4A, right hand panel). Both effects were positively correlated with age, i.e., younger adults generally showed lower BOLD signal in M1 and higher inhibition values, whereas higher M1 BOLD signal and lower inhibition values were mainly observed in the older adults, suggesting that increased brain activity in the "non-active" hemisphere was associated with decreased ability of the "active" hemisphere to inhibit the "non-active" hemisphere (Fig. 4B).

The aforementioned observations may partly explain the manifestation of increased coordination interference (e.g., phase wandering and phase transitions) in older adults during performance at higher movement speeds (Sosnoff and Newell, 2011; Temprado et al., 2010). For example, it is expected that older adults who show lower interhemispheric inhibition would also present increased bilateral brain activity during performance of high-frequency unilateral movements with upper and/or lower limbs. Likewise lesser capacity to modulate IHI as a function of task is expected to increase bimanual interference as, for example, in tasks where limbs are required to move with different frequency ratios (e.g., Sisti et al., 2011). Importantly, Talelli et al. (2008a,b) reported that age-related declines in the ability to regulate inhibition were found only for LIHIs but not for SIHIs. This finding suggests that the decreased ability to modulate M1-M1 IHIs in the aging brain may not be only due to degeneration of callosal fibres that directly connect the two primary motor cortices. Instead, the declined ability to modulate LIHIs hints that regulation of inhibition between the two motor cortices involves transcallosal interactions that expand beyond M1, for example projections from the contralateral PMd (Hinder et al., 2012) or (pre-)SMA (Neubert et al., 2010). In addition, the reduced ability to modulate LIHIs in the older adults may well be attributed to neurodegenerative processes within those regions, for example, decrease of GABA levels (Gao et al., 2013).

4. Inhibitory control and age-related changes in brain structure

It is well accepted that structural changes in the aging brain may at least partly contribute to the decline of motor performance in the general healthy older population. These structural changes are normally characterized by a decrease in white matter microstructural organization (O'Sullivan et al., 2001; Pfefferbaum et al., 2005; Salat et al., 2005; Sullivan et al., 2001) and gray matter loss (Good et al., 2001; Resnick et al., 2003; Ziegler et al., 2012; see review, Seidler et al., 2010). DTI is a non-invasive magnetic resonance technique that provides information about microstructural organization of white matter (myelinated) bundles by measuring the directionality of water diffusion (Basser et al., 1994). Evidence from recent studies of Rushworth's group (Buch et al., 2010; Neubert et al., 2010), using DTI in conjunction with dual-site TMS protocols, clearly showed that individual differences in the microstructure of the brain motor network do affect the dynamics of corticospinal excitability. For example, by using diffusion-weighted magnetic resonance image scans alongside with TMS, Buch et al. (2010) showed that inter-subject differences in the facilitation-inhibition contrast during a task which required action reprogramming of a goal-directed action were correlated with fractional anisotropy (FA) of white-matter structures of ventral-prefrontal, premotor, and/or intraparietal brain regions in healthy young adults. Further evidence for correlations between individual differences in white-matter anisotropy and inhibitory control in healthy young individuals was reported in a second study from the same group (Neubert et al., 2010). These authors showed that individual differences in inhibitory interactions between the pre-SMA and M1 could be predicted by the mean FA of white-matter connections between

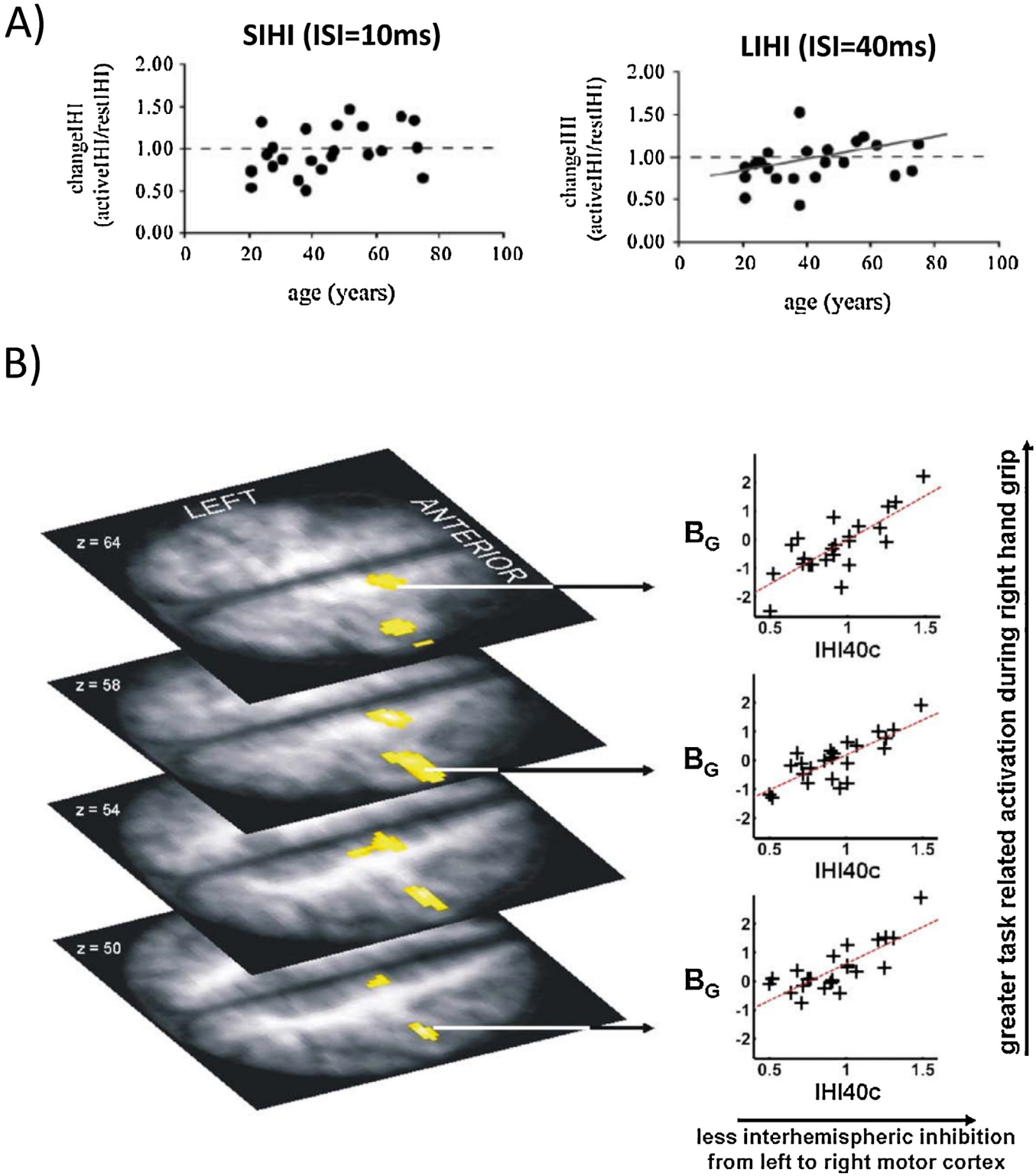

Fig. 4. Interhemispheric inhibition and age-related differences in brain activation. (A) The associations between the neurophysiological predictors for interhemispheric inhibition (SIHI and LIHI), age, and brain activation reported by Talleli and colleagues (Talelli et al., 2008a,b). Age was significantly correlated with LIHI (ISI = 40 ms) but not SIHI (ISI = 10 ms). Definitions: restIHI = IHI measured with both hands relaxed; activeIHI = IHI measured during a tonic contraction of the dominant hand; changeIHI = activeTMS/restTMS; changeTMS < 1 indicate stronger IHI at the active condition. Illustration was reproduced from Talelli et al. (2008b) with permission. (B) Brain activation during right hand grip (BG) is greater in left (ipsilateral) sensorimotor cortex and supplementary motor area in subjects with less interhemispheric inhibition (where a greater value for IHI40c represents less interhemispheric inhibition) from left to right motor cortices. The significant voxels ($p < 0.05$, corrected) are overlaid onto the mean normalized T1-weighted structural image obtained from all subjects (right hand panel). Illustration was reproduced from Talelli et al. (2008a) with permission.

the aforementioned regions. Relating changes in the microstructural organization of the aging brain to age-related declines in the ability to modulate inhibition is, therefore, a necessary step for understanding the mechanisms which underlie performance deficits in healthy aging.

Regulation of IHI may depend, in this respect, on the integrity of the corpus callosum (CC) which plays a critical role in the functional integration of large scale brain networks that mediate interhemispheric communication. Since disintegration of the motor callosal fibers is expected to disrupt connectivity among brain regions, one would expect to find an association between degraded coordination performance and age-related changes in IHI. Some evidence to support this view comes from Fling and Seidler (2012a) who assessed transcallosal inhibition and microstructural integrity of interhemispheric fiber tracts connecting the two primary motor cortices in a single experimental design. Findings, however, were somewhat surprising. In line with evidence from many other studies, Fling and Seidler (2012a) showed that a better microstructural organization of CC fiber tracts in healthy older adults (Fling et al., 2011b), as well as in patients with leukoaraiosis (Frederiksen et al., 2011; Jokinen et al., 2012; Lanza et al., 2013; Ryberg et al., 2011), is beneficial for performance. Importantly, the results from Fling and Seidler (2012a) study revealed that (1) higher levels of transcallosal inhibition (i.e., longer iSPs) predicted better callosal microstructural organization of the CC (i.e., higher FA values) in young adults but (2) higher levels of transcallosal inhibition predicted poorer performance in older adults. In other words: superior structural integrity was positively associated with stronger transcallosal inhibition in young adults, whereas this relationship was negative in older adults who also showed a negative relationship between transcallosal inhibition and performance. Taken together, it was proposed that older adults who maintained interhemispheric fiber tract integrity may rely less on transcallosal inhibition as a compensation strategy for performance declines (Fling and Seidler, 2012a).

Findings from other TMS studies using double-site TMS protocol provide further evidence that the declines in the ability to modulate transcallosal inhibition may not be directly attributed to microstructural organization of the CC. For example, observations from studies where IHI inhibition was monitored in older adults with double-site TMS showed that the ability to regulate SIHI (which directly reflects M1-M1 inhibition) is either preserved (Talelli et al., 2008a,b) or exhibited only slight declines with aging (Hinder et al., 2012). Rather, task-related declines in the ability to regulate IHI (Hinder et al., 2012; Talelli et al., 2008a,b) are more prominent in LIHI, suggesting that decreased integrity of callosal fibers is not a limiting factor for regulation of interhemispheric inhibition between homologous motor centers. Interestingly, age-related changes in the microstructural organization of the CC are also non-uniform in that anterior segments of the CC are more prone to degeneration than posterior parts (e.g., Coxon et al., 2012; Pfefferbaum et al., 2005; Serbruyns et al., 2013). This may partly explain the observations by Talelli et al. (2008a,b) that LIHIs between the two motor cortices (which are believed to be mediated via indirect projections combining anterior, posterior and/or subcortical brain regions) were more affected by aging than SIHIs which are believed to be mediated by direct callosal pathways between the two motor cortices.

Alternatively, age-differences in interhemispheric interactions involving LIHI but not SIHI could be taken as markers for the integrity of interhemispheric interactions between non-primary motor and/or prefrontal regions and the M1 of the opposite hemisphere via indirect (subcortical) pathways. Therefore, white matter substructures other than the CC should also be considered. Possible candidates are the white matter bundles connecting the (pre-)SMA with the right IFC and the subthalamic nucleus (STN). The role of these brain regions in the inhibitory control of action and cognition is well documented (e.g., Aron and Poldrack, 2006; Duann et al., 2009; see review, Aron et al., 2007). Importantly, parts of the brain network that regulate inhibition are located in the prefrontal cortex which is more prone to age-related structural changes than posterior areas (e.g., Coxon et al., 2012; Pfefferbaum et al., 2005). Indeed, recent structural imaging studies clearly show that age-related changes in the microstructural organization of the prefrontal-basal ganglia network are associated with a reduced ability to actively prevent movements when a "stop" is delivered after a "go" (Coxon et al., 2012; Hu et al., 2012, 2013). Particularly in older adults, higher microstructural organization of white matter bundles that connect the right IFC, pre-SMA, and STN predicts successful performance of switching and stopping behavior.

In addition to breakdown of the myelin sheath around the axon of neurons, structural changes in the aging brain also consist of shrinkage in soma size, reduction in the complexity of dendrite arborization and length (Dickstein et al., 2007), interneuron loss (Stanley et al., 2012), and alteration in the number of GABA receptors (e.g., Gleichmann et al., 2012) which is generally a sign of gray matter atrophy (see review, Kumar and Foster, 2007). These changes are likely associated with impaired ICI and IHI in the aging brain, e.g., by decreasing the number of active GABA-ergic inhibitory interneurons (both $GABA_A$ and $GABA_B$) within brain centers that control inhibition. Finally, a recent study, using magnetic resonance spectroscopy (1H-MRS) detected declines in GABA levels in healthy older participants (Gao et al., 2013). This observation could explain the reported declines in both resting-state and task-related $GABA_A$-mediated activity in the M1 of older adults (Heise et al., 2013). A promising avenue for further research would be linking the declines in GABA levels with age-related changes in the ability to modulate ICI and IHI in the aging brain as has been suggested in this review.

5. Inhibition and changes in brain activity

Evidence from many fMRI studies indicates that older adults recruit additional cortical and subcortical areas compared to young adults for the performance of the same motor tasks (Boudrias et al., 2012; Calautti et al., 2001; Goble et al., 2010; Heuninckx et al., 2005, 2008, 2010; Mattay et al., 2002; Swinnen et al., 2011; Talelli et al., 2008a; Ward and Frackowiak, 2003; Ward et al., 2008). Generally, increased brain activation has been considered as "compensatory" (e.g., Cabeza, 2001) since such activity is often positively correlated with performance. Compensatory brain activation is normally observed in high performing older adults during complex motor tasks and in regions that are generally less activated by young adults. Interestingly, this increased activation is often (but not exclusively) seen in prefrontal brain regions such as the IFC and/or (pre-)SMA (Goble et al., 2010; Heuninckx et al., 2008) that are classically involved in the suppression of prepotent response tendencies. An interesting question, therefore, is the extent to which this increased activation is associated with the recruitment of extra inhibitory pathways or elevated activity in inhibitory brain networks? One way to address this question is linking the observation of Heuninckx et al. (2008) where increased BOLD fMRI signal predicted better performance, with the observations of Fujiyama et al. (2012a) who showed an increased cortical inhibition in M1 in high- but not low-performing older adults.

Notably, both studies used the same behavioral task (i.e., the non-isodirectional patterns with ipsilateral hand and foot) and showed elevated cortical inhibition (Fujiyama et al., 2012a) and increased BOLD responses (Heuninckx et al., 2008) in high-performing older individuals. In contrast, older individuals who showed lower levels of cortical inhibition and lower levels of BOLD response were also those who performed worst. Interestingly,

observations from an early study by the same authors (Heuninckx et al., 2005) indicated that increased BOLD signal in cortical regions of the brain during execution of the non-isodirectional (non-preferred) mode was especially pronounced in secondary motor areas (specifically, (pre-)PMd and (pre-)SMA), whereas these brain areas were less active during execution of the isodirectional (preferred) mode of coordination. Fujiyama et al. (2009, 2012a) also reported longer SPs during the non-isodirectional mode as compared to the isodirectional mode, which can be interpreted as an increased activation of $GABA_B$-ergic inhibitory interneurons. Both effects may represent a signature for suppression of prepotent response tendencies (i.e., the tendency to shift from non-isodirectional foot-wrist coordination to the isodirectional coordination mode). Thus, the speculation emerges that the increased activity of prefrontal/premotor brain areas during the performance of the non-isodirectional movements (observed by Heuninckx et al., 2008) is partly related to an increased recruitment of inhibitory motor pathways in high-performing older individuals (reported by Fujiyama et al., 2012a) whereas low-performing older adults may lack the capacity to recruit extra inhibitory resources.

The aforementioned hypotheses should be taken, nonetheless, with caution. Indeed, some of the brain areas showing increased activation during performance of the non-isodirectional movements, such as the IFC and PMd (Heuninckx et al., 2005, 2008), are directly connected with the primary motor cortex (Boudrias et al., 2012; Neubert et al., 2011). Other prefrontal or secondary-motor regions such as the (pre)SMA and DLPFC appear to regulate M1 excitability via subcortical or indirect cortico-cortical loops (Aron et al., 2007; Aron and Poldrack, 2006; Coxon et al., 2010, 2012). Alternatively, elevated activation of prefrontal or parietal brain areas in the high-performing older individuals may be the result of increased demands on memory (Bangert et al., 2010; Lewis and Miall, 2003; Summers et al., 1981), increased deployment of attention (Boisgontier et al., 2012; Coxon et al., 2010; Fujiyama et al., 2010; Heuninckx et al., 2004; Hiraga et al., 2004, 2005; Van Impe et al., 2011; see review, Boisgontier et al., 2013) and/or increased reliance on sensory information processing (Boisgontier and Nougier, 2013; Heuninckx et al., 2005, 2010; Serrien et al., 2000; Van Impe et al., 2009).

Increased brain activation in older adults may also be associated with dysfunctional brain activity which is generally characterized by activation spreading from active to non-active motor regions (e.g., Boudrias et al., 2012; Talelli et al., 2008a). Therefore, by relating functional brain imaging metrics and task-related changes in IHI metrics, it is possible that a link may be established between poor inhibitory interactions and increased dysfunctional activation spreading from the active M1 to primary and/or secondary motor areas in the contralateral hemisphere (Talelli et al., 2008a; Ward, 2006). Further evidence, linking inferior transcallosal inhibition in older adults with positive BOLD changes during motor activity, has come from recent studies of McGregor et al. (2013, 2011). Such dysfunctional activation spreading is not predicted to be associated with higher performance.

6. Do interventions make a difference?

We have argued that declines in inhibitory functions with aging are related to differences in motor performance. The ability to regulate inhibition declines in healthy aging due to multiple degenerative processes in GABA-ergic or cholinergic neurotransmission systems (as described in Section 3). Evidence from animal models, however, suggests that pharmacological intervention could compensate for this decline. For example, observations from a study on primates (Leventhal et al., 2003) showed that the administration of muscimol (a $GABA_A$ receptor agonist) improved visual functions in older animals, presumably via the up-regulation of intracortical inhibitory processes. Yet, there is no clear line of evidence to suggest that pharmacological interventions targeting the GABA-ergic system may help to improve motor functions in healthy human older adults. Further investigation as to whether the pharmacological interventions improve inhibitory control of movements in the general healthy population is warranted.

There is some evidence that alterations in brain structure and function with advancing age can be delayed or even reversed and skills can be revived by training-induced neuroplastic changes (e.g., Erickson et al., 2007). More specifically, recent work has shown that learning a new skill induces plastic changes in grey and white matter structure in young adults (Scholz et al., 2009; Taubert et al., 2011) and grey matter increase in older adults (Boyke et al., 2008). The basic assumption is that these structural changes are the result of adaptation based on relative use and activity (use-dependent plasticity), whereby such changes in functional processing induces the structural changes. Related changes have also been observed with the use of TMS, showing modulation of cortical excitability and inhibitory function after training (Koeneke et al., 2006).

Other possible interventions consist of non-invasive brain stimulation techniques, electrical or magnetic stimulation and cortical stimulation combined with peripheral stimulation. In particular transcranial direct current stimulation (tDCS) may have high clinical potential since the device is inexpensive and operation is very simple. For example, anodal tDCS (atDCS) over the DLPFC has been reported to transiently improve cognitive functions (e.g., Javadi and Walsh, 2012; Leite et al., 2011) and supports learning (e.g., Foerster et al., 2013; Reis and Fritsch, 2011). There is also evidence that tDCS over M1 in healthy older adults improves motor performance (Hummel et al., 2010; Zimerman et al., 2013), highlighting the potential benefit of tDCS. Interestingly, it has also been demonstrated that application of atDCS improves the efficiency of inhibitory control (and enhances cognitive control of action) (Boggio et al., 2006; Fecteau et al., 2007). The question remains open whether long term atDCS-supported training can promote changes in brain structure, alleviate age-related declines in the control of inhibition and improve cognitive control of action more effectively than training on its own. Further studies in this domain are essential for uncovering age-related changes in inhibitory recruitment processes and provide a foundation for intervention programs that promote functional independence, a goal with considerable social and economic impact.

7. Conclusions, limitations and further directions

Over the past five years TMS has been increasingly used as a non-invasive method to monitor age-related changes in the integrity of inhibitory functions responsible for motor decline in healthy aging. In the present review we outlined evidence from recent TMS studies linking poor inhibitory control with declined performance of voluntary movements in healthy older individuals (Cuypers et al., 2012; Fling and Seidler, 2012a; Fujiyama et al., 2009, 2012a; Heise et al., 2013; Hinder et al., 2012; Levin et al., 2011; McGregor et al., 2013, 2011). Overall, these studies indicate the possible contribution of the ability to modulate inhibitory function to preserved motor performance in healthy aging. Specifically, observations from the studies of Fujiyama et al. (2012a,b), Heise et al. (2013), and Hinder et al. (2012) suggest that successful performance of a motor task in older adults is related to the capacity to modulate inhibition through the $GABA_A$- and $GABA_B$-ergic neurotransmission systems. Interactions between GABA-ergic and other neurotransmission systems should, nonetheless, be considered as well. Although these findings show a consistent pattern, there is still a need for further research to substantiate the association between reduced control

of inhibition and age-related changes in performance. One necessary step towards generalization of the findings reported here is to link them with other hallmarks of the aging CNS that have also been associated with motor performance declines, such as declines in brain structural metrics and changes in functional brain activity.

While this review highlights the advantages of TMS as an important research tool to explore age-related changes in the integrity of the brain networks that control movements, one should not overlook its limitations. First, the TMS techniques discussed in this review cannot be used to assess inhibitory pathways that do not project to M1. Given that inhibition of action is controlled by brain networks that span beyond M1, using TMS as the only method to evaluate inhibitory functions in the aging brain will limit our understanding of the role of inhibitory mechanisms in motor control. Second, only a small number of studies have used TMS to explore the integrity of the inhibitory motor network in the aging brain and only a limited number of motor tasks have been examined in these studies. More studies are needed to obtain a more comprehensive picture of TMS techniques and subgroups of the healthy older population (e.g., active versus sedentary older adults, males versus females, etc.). Furthermore, the current literature still lacks a critical body of evidence that allows systematic and meta-analysis type reviews.

The research summarized in this review provides evidence for presumptive relationships between declines in the inhibitory control of movements and other biomarkers of aging which reflect changes in structural and functional brain metrics (Fling et al., 2011a) in the general healthy population. An important challenge for the near future is to make use of a complementary array of brain measurement techniques, such as MRI and TMS techniques, to further our understanding of the aging brain in action.

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