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Network interactions underlying mirror feedback in stroke: A dynamic causal modeling study

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ABSTRACT

Mirror visual feedback (MVF) is potentially a powerful tool to facilitate recovery of disordered movement and stimulate activation of under-active brain areas due to stroke. The neural mechanisms underlying MVF have therefore been a focus of recent inquiry. Although it is known that sensorimotor areas can be activated via mirror feedback, the network interactions driving this effect remain unknown. The aim of the current study was to fill this gap by using dynamic causal modeling to test the interactions between regions in the frontal and parietal lobes that may be important for modulating the activation of the ipsilesional motor cortex during mirror visual feedback of unaffected hand movement in stroke patients. Our intent was to distinguish between two theoretical neural mechanisms that might mediate ipsilateral activation in response to mirror-feedback: transfer of information between bilateral motor cortices versus recruitment of regions comprising an action observation network which in turn modulate the motor cortex. In an event-related fMRI design, fourteen chronic stroke subjects performed goal-directed finger flexion movements with their unaffected hand while observing real-time visual feedback of the corresponding (veridical) or opposite (mirror) hand in virtual reality. Among 30 plausible network models that were tested, the winning model revealed significant mirror feedback-based modulation of the ipsilesional motor cortex arising from the contralesional parietal cortex, in a region along the rostral extent of the intraparietal sulcus. No winning model was identified for the veridical feedback condition. We discuss our findings in the context of supporting the latter hypothesis, that mirror feedback-based activation of motor cortex may be attributed to engagement of a contralateral (contralesional) action observation network. These findings may have important implications for identifying putative cortical areas, which may be targeted with non-invasive brain stimulation as a means of potentiating the effects of mirror training.

1. Introduction

The use of mirror visual feedback (MVF) for neurorehabilitation of stroke impairment has grown in the past 20 years, however, little is known about the underlying neurophysiological mechanisms by which MVF may modulate activity in the ipsilesional sensorimotor cortex, and hence aid recovery (Deconinck et al., 2015). We have recently shown that virtual MVF of motion of the non-affected hand can elicit significant activation of the ipsilesional sensorimotor cortex in the absence of movement of the affected hand (Saleh et al., 2014). Critically, we showed that this activation overlapped with areas involved in volitional control of the affected hand. These data, therefore, provide a neural basis for virtual mirror feedback, by showing that mirror feedback can activate ipsilesional motor-related hubs that are important for the recovery process. The findings about the neural underpinnings of mirror feedback are encouraging particularly in light of recent clinical studies showing that MVF may show promise in restoring function after stroke (Yavuzer et al., 2008; Dohle et al., 2009; Thieme et al., 2012, 2013). The goal of this project is to fill this gap by identifying the neural network and mechanisms by which the ipsilesional motor cortex is facilitated by MVF.

The key question we ask is, what is the source of the signal mediating MVF-elicited facilitation of ipsilesional sensorimotor cortex? Review of available literature posits two competing hypotheses that we aim to test.

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The first hypothesis predicts that MVF may mediate the interhemispheric interactions between the motor cortices. Support for this prediction is rooted in a magnetoencephalography (MEG) study or chronic stroke patients that found movement-related beta desynchronization between motor cortices to be less lateralized during bilateral hand movement performed with MVF than when performed without MVF (Rossiter et al., 2015). Additional support for this hypothesis arises from literature on the neural basis of cross-activation, a phenomenon akin to overflow of activation from one hemisphere to the other during vigorous movement (Lee et al., 2010; Sehm et al., 2010; Reissig et al., 2014). In apparent contradiction, studies using TMS to directly measure changes in interhemispheric inhibitory (IHI) balance resulting from MVF have indicated either a reduction (Carson and Ruddy, 2012; Avanzino et al., 2014), or no change in IHI (Lappchen et al., 2012; Nojima et al., 2012; Lappchen et al., 2015). Therefore, it remains unclear if it is indeed the contralesional motor cortex that modulates the ipsilesional motor cortex to mediate the MVF facilitation. Here, we directly investigate this prediction by using a unilateral movement with and without MVF, to test if the source of MVF-elicited facilitation of the inactive (ipsilesional) M1 arises from the active (contralesional) motor cortex.

The second hypothesis predicts that MVF may activate a bilateral action observation network, which in turn modulates the inactive motor cortex. Here, we operationally define the action observation network (AON), according to published work, as a bilateral fronto-parietal network that is activated when primates or humans observe biological actions (Buccino et al., 2001; Howatson et al., 2013) such as the focused observation of real or virtual hand motion (Perani et al., 2001; Suchan et al., 2007; Chong et al., 2008a, 2008b; Adamovich et al., 2009). Parietal regions comprising the AON have been shown to be involved in transcallosally communicating with frontal areas for visuomotor remapping (Blangero et al., 2011; Pisella et al., 2011; Zult et al., 2014), and to modulate activation of M1 (Koch et al., 2009; Grefkes and Fink, 2011). Thus, it is possible that MVF-mediated facilitation of ipsilateral M1 may arise from selective regions comprising the AON. In support of this prediction is recent fMRI evidence that parts of the AON network, including inferior and superior parietal lobules, superior temporal gyrus, and sensorimotor areas, are recruited in MVF paradigms (Michielsen et al., 2011a; Hamzei et al., 2012; Saleh et al., 2014). Given the known parietal cortex involvement in movement observation and visuomotor integration, it is possible that MVF-mediated changes in motor cortex excitability arise from the AON network, perhaps via parietal-M1 modulation.

The above two hypotheses bear significant importance for stroke patients who have persistent undesirable increases in IHI from contralesional to ipsilesional M1 during hand movement (Murase et al., 2004) and weakened parietal-M1 interactions (Grefkes and Fink, 2011; Takeuchi et al., 2012). Empirical evidence suggests that the activation of these regions (Grefkes and Fink, 2011; Rehme et al., 2011, 2012), and restored interactions between these regions measured as functional and effective connectivity are important predictors of recovery (He et al., 2007; Carter et al., 2010; Wang et al., 2010; van Meer et al., 2012; De Vico Fallani et al., 2016). Therefore, understanding the MVF network interactions may unveil if mirror feedback has the potential to engage circuits in a manner that may be favorable for recovery.

The focus of the current investigation was to build on our understanding of the neural mechanisms underlying virtual MVF, by analyzing the effective connectivity in our previously published dataset (Saleh et al., 2014). We used Dynamic Causal Modeling (DCM) to model interactions among activated brain regions and draw inferences on the connectivity strength within this neural network (Friston et al., 2003). Classical deterministic bilinear DCM allows testing the changes in a neural state of a brain region in terms of changes in intrinsic neurophysiological interactions among brain regions independent of the experimental stimulus (input), extrinsic interactions between brain regions modulated by the input, and the direct influence of the input on each region's activity.

2. Materials and methods

2.1. Participants

This study included fifteen right-handed (Oldfield, 1971) subjects, with hemiparesis due to stroke (5 right-hemiplegics, 5 females, mean age 54 ± 12 years, range: 37–74 years old). The subjects participated after signing informed consent approved by the institutional review board. Two subjects were excluded from analysis. One subject was excluded for excessive head motion and another because the brain lesion encompassed the sensorimotor cortex (see Table 1 for clinical information).

2.2. Experiment task and visual feedback

During the experiment, subjects lay in the scanner and wore an MRI-compatible instrumented glove recording 14 joint angles of the hand in real time. Subjects viewed back-projected visual stimuli reflected in a mirror within the scanner bore. In four consecutive scanning runs, subjects moved the non-paretic hand and watched the feedback in the VR environment. Movement in each trial was cued by a text prompt “move”, cuing the subject to perform an out-and-back finger movement with a short pause at the target location, followed by a text prompt “rest”, cuing the subset to rest at the start position and await the next trial. The “move” prompt was displayed for the duration of the trial event (5 s), and the “rest” prompt was displayed for the duration of the rest period (random 4–7-sec jittered). Subjects were instructed to complete the movement within the “move” epoch. Each scanning run included eight repetitions of four randomly interleaved visual feedback conditions: 1) movement of the ipsilateral VR hand model (veridical-feedback condition), 2) movement of the contralateral VR hand model (mirror-feedback condition), 3) rotation of an ellipsoidal object ipsilateral to the non-paretic moving hand (CTRL, veridical-feedback condition), and 4) rotation of an ellipsoidal object contralateral to the moving hand (CTRL, mirror-feedback condition). The hardware and experiment setup are explained in more detail in our previous publication (Saleh et al., 2014). In this study, we investigated the effect of conditions 1 and 2 on the effective connectivity within the sensorimotor network (Fig. 1).

Table 1
Subjects'clinical information.

Subject	Age	Gender	Months	CMA/CMH	Lesion
S1	63	F	53	6/4	L cortical
S2	55	M	41	5/4	L subcortical
S3*	49	M	144	5/4	L subcortical
S4	74	M	9	6/6	R cortical
S5	70	F	96	7/5	R subcortical
S6	58	M	132	5/4	R cortical
S7	37	M	92	4/3	R subcortical
S8	69	F	18	7/7	R subcortical
S9	68	M	78	6/6	R cortical
S10	48	F	148	4/3	R cortical
S11*	41	F	70	6/6	R cortical
S12	43	M	11	4/4	L subcortical
S13	41	M	158	6/6	L cortical
S14	53	M	156	6/6	R subcortical
S15	39	F	14	4/3	R cortical

CVA, cerebrovascular accident; CMA, Chedokee-McMaster Motor AssessmentArm Scale; CMH, Chedokee-McMaster Motor Assessment Hand Scale; dWMFT, Distal Wolf Motor Function Test; L, left; R, right; Months, time since CVA in months. Asterisks highlight the subjects excluded from the analysis.