1 **Choice of Contact Points Modulates Sensorimotor Cortical**
2 **Interactions for Dexterous Manipulation**

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13

15 **ABSTRACT**

16 Humans are unique in their ability to perform dexterous object manipulation in a wide
17 variety of scenarios. However, previous work has used a grasping context that
18 predominantly elicits memory-based control of digit forces by constraining where the
19 object should be grasped. For this 'constrained' grasping context, primary motor cortex
20 (M1) is involved in storage and retrieval of digit forces used in previous manipulations. In
21 contrast, when choice of digit contact points is allowed ('unconstrained' grasping),
22 behavioral studies revealed that forces are adjusted, on a trial-to-trial basis, as a function
23 of digit position. This suggests a role of online feedback that detects digit position, rather
24 than memory, for force control. However, despite the ubiquitous nature of unconstrained
25 hand-object interactions in activities of daily living, the underlying neural mechanisms are
26 unknown. Using non-invasive brain stimulation and electroencephalography, we found the
27 role of M1 to be sensitive to grasping condition. While confirming the role of M1 in storing
28 and retrieving learned digit forces and position in 'constrained' grasping, we also found
29 that M1 is involved in modulating digit forces to digit position in unconstrained grasping.
30 Furthermore, we found that digit force modulation to position relies on sensorimotor
31 integration mediated by primary sensory cortex (S1) and M1. This finding supports the
32 notion of a greater contribution of somatosensory feedback of digit position in
33 unconstrained grasping. We conclude that the relative contribution of memory and online
34 feedback based on whether contact points are constrained or unconstrained modulates
35 sensorimotor cortical interactions for dexterous manipulation.

36   **INTRODUCTION**

37   Dexterous object manipulation is a hallmark of human evolution (1–4). Co-adaptation of

38   anatomical features and sensorimotor control mechanisms (5) have made dexterous

39   manipulation a versatile means of interacting with the environment, while inspiring (6)

40   and challenging (7) efforts to build dexterous robotic and prosthetic hands. The ability to

41   skillfully use our hands depends on cortical mechanisms supporting several

42   sensorimotor processes (4, 8–10), including integration of sensorimotor memory of

43   previous hand-object interactions with online sensory feedback (11, 12). Although the

44   role of motor and parietal cortices in this sophisticated interplay has been extensively

45   studied (13–17), this work has drawn an incomplete picture of these cortical

46   mechanisms. Research over the past three decades has focused on the control of digit

47   forces through a paradigm based on grasping objects at visually-cued contacts

48   (*constrained* grasping) (12, 18). These studies have shown that subjects use the same

49   digit forces over consecutive trials by relying on a sensorimotor memory (19–22). Upon

50   lifting the object, online sensory feedback is used to assess the accuracy of the force

51   plan and update the sensorimotor memory of digit forces for future manipulations if an

52   error occurs, e.g., object slip or tilt (11, 12, 19, 20, 22). The 'constrained grasping'

53   paradigm, while providing significant insights into neural control of object manipulation,

54   has neglected a critical component of sensorimotor control that is fundamental to natural

55   hand-object interactions: choice of contact points.

56   When individuals can choose where to grasp an object (*unconstrained* grasping) – as

57   it happens in many activities of daily living –, the central nervous system is presented

58   with unique challenges: as there are no visual cues constraining where to grasp an

59   object, unconstrained grasping is characterized by greater trial-to-trial variability of digit

60   position than constrained grasping; this occurs even after the object dynamics have

61   been fully learned (23–28). If control of digit forces in unconstrained grasping relied

62   predominantly on sensorimotor memory, the same forces would be applied on each trial

63   regardless of contact point. This behavior would lead to task failure. Remarkably, skilled

64   manipulation can still be accurately performed because participants modulate digit

65   forces as a function of digit position on a trial-to-trial basis (25–27). This evidence

66   suggests that individuals do not rely primarily on memory of digit forces in unconstrained

67   grasping. We have proposed that the predominant mechanism involves online feedback

68   of digit position to change the force distribution every time an object is grasped at novel

69   contact points (25, 26).

70   The ability to modulate digit forces to position raises the question as to whether

71   adding choice of digit placement to manipulation would elicit distinct interactions among

72   cortical grasp regions. Allowing choice of contact points has revealed differences in brain

73   activation (29) and corticospinal excitability (30). However, the causal role of primary

74   motor and somatosensory cortices (M1 and S1, respectively) for the control of digit

75   forces and position remains to be established. The present work was designed to

76   address this issue by combining brain stimulation, electroencephalography, and a

77   dexterous manipulation paradigm we have validated in our previous studies.

78   Based on the above behavioral evidence (25–27) we hypothesized that, in

79   unconstrained grasping, M1 and S1 are both involved in digit force-to-position

80   modulation, each area being responsible for distinct functions: S1 would relay

81   somatosensory feedback about digit position to M1, while M1 would process this

82   feedback to modulate digit forces. Therefore, we predicted that a virtual lesion to M1 or

83   S1 in unconstrained grasping should interfere with digit force-to-position modulation. In

84   contrast, in constrained grasping a virtual lesion to M1 should only impair retrieval of

85   digit forces used in previous manipulations. This hypothesis is based on evidence

86   implicating M1 with building, storing, and retrieving sensorimotor memories of grasp

87   forces in constrained grasping (15, 17). Lastly, based on previous work (31) we

88   expected a virtual lesion to S1 to have no effect on digit forces.

89   Our experiments uncovered important functional differences in brain dynamics over

90   M1 and S1 between the two grasp contexts. We first demonstrate that effective

91   connectivity from S1 to M1 is significantly stronger in unconstrained than constrained

92   grasping. This result is consistent with our hypothesis that S1 provides inputs to M1 for

93   scaling digit forces. We confirmed these hypothetical roles of S1 and M1 through virtual

94   lesions. As anticipated, stimulation of S1 disrupted digit force scaling only in

95   unconstrained grasping. Stimulation of M1 during unconstrained grasping interfered with

96   digit force-to-position modulation and led participants to rely on previously-used digit

97   forces. In contrast, stimulation of M1 during constrained grasping impaired participants'

98   ability to retrieve forces used in previous manipulations. These results provide

99   comprehensive support for our theoretical framework of dexterous manipulation.

100

101   **RESULTS**

102   For both constrained and unconstrained grasp contexts (*con* and *uncon*, respectively),

103   the task consisted of grasping and lifting a sensorized object using the thumb and index

104   fingertip. The task's goal was to minimize object roll during lift. Participants achieved this

105   goal by exerting a compensatory torque (T_{com}) on the object prior to object lift to

106   counteract the object's external torque (T_{ext}) caused by its asymmetrical mass

107   distribution (Fig. 1A; eq. 1, Materials and Methods). As expected from our previous work,

108   we found a significant negative correlation between T_{com} and peak object roll (see

109   Materials and Methods). Therefore, for brevity we focus on T_{com} as measure of

110   anticipatory grasp control and manipulation performance.

111   The *con* and *uncon* grasp contexts differed only in terms of whether object contact

112   locations were visually cued or could be chosen by the subject. As expected, we found

113   that subjects in *con* and *uncon* groups learned within the first three trials to generate

114   T_{com}. However, digit load forces were significantly correlated with trial-to-trial changes in

115   digit position only for *uncon* grasping (*SI Appendix*, S3). To determine the extent to

116   which the role of M1 and S1 is grasp-context dependent, we conducted

117   electroencephalography (EEG) and transcranial magnetic stimulation (TMS)

118   experiments (Fig. 2A,B).

119

120   **Sensorimotor cortical activity is sensitive to grasp context**

121   The EEG experimental design aimed at removing significant differences in digit position,

122   forces, and torques at object lift onset across the two grasp contexts (see Materials and

123   Methods). This was confirmed by statistical analyses revealing that digit force and

124   position distributions at object lift-off were statistically indistinguishable in *con* versus

125   *uncon* grasping (all *P* > 0.62).

126   We recorded EEG and quantified source current density power over precentral and

127   postcentral regions (*SI Appendix*, S2). Source power was computed from contact to

128   object lift onset for all trials from both grasp contexts. Importantly, EEG *s*ource

129   power was significantly larger during *uncon* than *con* grasping over both M1 and S1

130   (main effect of *Group*: $F_{1,21}$ = 379.6 with $\eta_p^2 = 0.95$ and 22.69 with $\eta_p^2 = 0.52$,

131   respectively; both *P* < 0.0001; Fig. 3A,B). Furthermore, statistical analysis used to

132   analyze Granger causal directed connectivity between M1 and S1 revealed a significant

133   interaction between the factors of grasp type (*con* versus *uncon*) and connectivity

134   direction (M1 to S1 versus S1 to M1) ($F_{1,21}$ = 3.87, *P* < 0.05, $\eta_p^2 = 0.16$). As predicted by

135   our framework, the effective drive was higher going from S1 to M1 during *uncon*

136   compared to *con* grasping (t_{21} = 2.53, *p* < 0.01, Cohen's d_z = 0.54), whereas there was

137   no significant difference in Granger causality from M1 to S1 for *con* and *uncon* grasping

138 (*P* > 0.05) (Fig. 3*C*). It is worth noting that while changes in power can correlate with

139 changes in connectivity, there is no strict dependency between the two. Therefore, these

140 results indicate the main cortical mechanism differentiating grasp contexts is not an

141 increased site activation, as both M1 and S1 increased in power from *con* to *uncon* (Fig.

142 3*B*). Importantly, the connectivity results indicate the main mechanism is an increased

143 information transfer from S1 to M1 in *uncon* grasping.

144   These findings support our hypothesis that the roles and interactions of M1 and S1

145 are dependent on grasp context, while raising the question of their functional roles. To

146 address the functional roles of M1 and S1 in *uncon* versus *con* grasping, we performed

147 TMS to induce virtual lesions to M1 and S1 using continuous theta burst stimulation

148 (cTBS) (Fig. 2*B*).

149

150 **A virtual lesion of M1 and S1 impairs execution of learned manipulation in a grasp**

151 **context-specific fashion**

152 On the first trial of the *Learn* block, subjects were unaware of the object's mass

153 distribution, as the object is visually symmetrical, and therefore exerted negligible T_{com}

154 (Fig. 4*A*; Learn 1, Fig. 4*B*). Consistent with previous work (25), all subjects quickly

155 learned to compensate for the object's mass distribution and generated the necessary

156 T_{com} over the remaining trials of the *Learn* block (main effect of *Block*: $F_{1,45}$ = 522.14, *P* <

157 0.0001, η_p^2 =0.92; Fig. 4*B*) similarly across experimental and control groups (no

158 significant *Group × Block* interaction: $F_{4,45}$ = 2.26 or main effect of *Group:* $F_{4,45}$ = 1.71,

159 both *P* > 0.08). Following learning, T_{com} was stable for all subjects during the remaining

160 *Learn* and *Pre* block trials across experimental and control groups (no significant *Group*

161 *× Block* interaction: $F_{7.85,88.32}$ = 0.8, no main effect of *Block*: $F_{1.96, 88.32}$ = 2.69, or no main

162 effect of *Group*: $F_{4,45}$ = 0.69; all *P*-values > 0.08; Fig. 4*B*; *SI Appendix*, S5).

163   We delivered cTBS to the M1 *con*, M1 *uncon*, S1 *con*, S1 *uncon*, and *Vertex* groups

164 immediately following the *Pre* block, but prior to the beginning of the *Post* block (Fig. 4).

165 We verified the effectiveness of our cTBS protocol using single-pulse TMS to measure

166 changes in corticospinal excitability in all groups (Fig. 2*B*; *SI Appendix*, S4 and Fig. S1).

167 We selected the vertex as a neutral control site to assess the specificity of cTBS-induced

168 effects on the control of our manipulation task following stimulation of M1 and S1.

169   Following cTBS over M1 and S1, but not vertex, subjects were unable to exert the

170 previously-learned T_{com} (significant *Group × Block* interaction: $F_{7.6, 85.53}$ = 4.36, *P* <

171 0.0001, η_p^2 = 0.28; main effect of *Block*: $F_{1.9, 85.53}$ = 33.55, *P* < 0.0001, η_p^2 = 0.43) (Fig.

172 4*B*). Specifically, on the first trial following cTBS (*Post1*), subjects in all experimental

173 groups exerted significantly smaller T_{com} than those in the *Vertex* group (Dunnett's t: all

174 *P*-values ≤ 0.004, 1.62 < Cohen's d < 2.82) , although T_{com} reduction was not

175 significantly different across experimental groups (Bonferroni's t: all *P*-values > 0.99).

176 However, the persistence of the cTBS effect on T_{com} during the *Post* block was

177 dependent on whether subjects performed the manipulation task in the *con* or *uncon*

178 condition and the cortical area targeted by cTBS. For the M1 *uncon*, S1 *uncon,* and S1

179 *con* groups, T_{com} impairment was short lived, returning to the same magnitude as T_{com}

180 exerted by the *Vertex* group at the end of the *Post* block (Dunnett's t: all *P*-values > 0.43;

181 Fig. 4*B*). In contrast, the drop in T_{com} for the M1 *con* group persisted until the end of the

182 *Post* block, as revealed by significantly smaller T_{com} relative to the *Vertex* group

183 (Dunnett's t: *P* = 0.016, Cohen's d = 1.12). Similar to the *Vertex* group, no difference in

184 task performance was found in all other control groups when comparing *Pre* and *Post*

185 blocks (*SI Appendix*, S5 and Fig. S2).

186   Because T_{com} results from the coordination of digit position (d_y), grip (F_{GF}) and load

187 (d_{LF}) forces (equation 1, Materials and Methods), we analyzed the extent to which virtual

188 lesions affected each of these variables for each experimental group using the same

189 subsets of trials as those used for the above T_{com} analysis. The similar reduction in T_{com}

190 observed on the first trial following cTBS could have been interpreted as a non-specific

191 effect on T_{com} variables regardless of grasp type and cortical area targeted by TMS.

192 However, the different time courses after cTBS (Fig. 4) indicate that digit position and

193 forces were highly sensitive to the grasp context and cortical area being stimulated.

194

195 **Constrained grasping: Virtual lesions of M1 and S1**

196 The M1 and S1 *con* groups learned T_{com} within the first few trials of the *Learn* block by

197 exerting a greater load force on the index finger than thumb (negative d_{LF}, equation 1,

198 Methods; this behavior has also been described in previous studies (25, 26, 32)).

199 Furthemore, participants consistently exerted the learned T_{com} throughout the blocks of

200 trials preceding cTBS.

201

202 **Disruption of M1 impairs retrieval of learned grip and load forces**

203 Following cTBS, M1 *con* participants were unable to retrieve and use the same digit

204 forces used in previous trials, such retrieval being a key feature of *con* grasping (19, 33).

205 This effect of cTBS started ~200 ms after contact, leading to significantly smaller digit

206   forces by the time the object was lifted (Fig. 5*A*, M1 *con* column) (main effect of *Block*:

207    $F_{2,18}$ = 14.30 ($\eta_p^2 = 0.61$), d_{LF} and 13.76 ($\eta_p^2 = 0.60$), F_{GF}; both *P* < 0.0001). d_{LF} and F_{GF}

208   on the first *Post* block trial were significantly smaller than on the late *Pre* block trials

209   (post1 vs. pre5: t_9 = −7.081 (Cohen's d_z = 2.24) and 3.936 (Cohen's d_z = 1.24),

210   respectively; both *P* < 0.003; Fig. 5*A*). Importantly, and in contrast to digit forces, d_y was

211   unaffected by cTBS (no main effect of *Block*, $F_{2,18}$ = 0.045, *P* = 0.956; $\eta_p^2 = 0.005$; Fig.

212   5*A,B*). These results indicate that the effect of cTBS on T_{com} in *con* grasping (Fig. 4) was

213   due to selective disruption of the retrieval of learned digit forces, while sparing the

214   control of visually-cued digit position. Note that the effects of cTBS on digit forces

215   persisted throughout all *Post* block trials (Fig. 5*B*; *SI Appendix*, S6 and Fig. S3).

216

217   **Disruption of S1 does not impair the modulation of digit forces or position**

218   Unlike the M1 *con* group, none of the T_{com} components was affected by cTBS in the S1

219   *con* group (no main effect of *Block*; d_{LF}: $F_{1.3,\ 11.74}$ = 2.6, F_{GF}: $F_{2,18}$ = 2.2, and d_Y: $F_{1.8,\ 16.5}$ =

220   3.5 respectively; all *P*-values > 0.05; Fig. 5*A*, S1 *con* column). These results indicate that

221   the effect of cTBS of S1 on *con* grasping was not due to a significant disruption of the

222   retrieval of learned digit forces or the control of visually-cued digit position. Therefore,

223   the reduction in T_{com} on the first post-cTBS trial (Fig. 4) was caused by a small, non-

224   significant effect on d_Y and its multiplicative effect on F_{GF} contribution to T_{com} (equation

225   1, Materials and Methods).

226

227   **Unconstrained grasping: Virtual lesions of M1 and S1**

228   Consistent with our previous behavioral work (25, 26, 32), M1 and S1 *uncon* groups

229   learned to exert T_{com} to counter the clockwise T_{ext} by exerting greater load force with the

230   the index finger and placing it higher than the thumb (negative d_{LF} and d_Y respectively;

231   equation 1, Methods). Unlike *con* grasping, d_{LF} and d_y significantly covaried across the

232   *Learn* and *Pre* block of trials (*SI Appendix*, S3).

233

234   **Disruption of M1 impairs control of learned digit position and modulation of load**

235   **force**

236   cTBS to M1 impaired subjects' ability to use similar digit positions learned in previous

237   *uncon* trials (main effect of *Block*: $F_{2,18}$ = 10.29, *P* = 0.001, $\eta_p^2 = 0.53$). Specifically, on

238   the first post-cTBS trial the vertical distance between thumb and index finger center of

239   pressure (d_Y) significantly decreased relative to the late *Pre* block trials (post1 vs pre5: t_9

240   = −4.384, P = 0.002, Cohen's d_z = 1.39) (Fig. 5A, M1 *uncon* column). Note that the large

241   change in d_Y caused by cTBS was not accompanied by a significant modulation of d_{LF} or

242   F_{GF} (no main effect of *Block*: $F_{2,18}$ = 5.27 and 0.106, respectively; both P > 0.05; both

243    $\eta_p^2 < 0.37$). This is an important observation, given that d_{LF} modulation to d_Y is a key

244   feature of *uncon* grasping which was found during *Learn* and *Pre Block* trials. Thus, the

245   effects of cTBS during *uncon* grasping were opposite to those found for *con* grasping:

246   virtual lesion to M1 impaired the control digit placement, but not digit forces. These

247   results indicate that the lack of modulation of d_{LF} to the cTBS-induced change in d_Y

248   caused the drop in T_{com} in the early trials of the *uncon* grasping condition (Fig. 4A).

249   However, on subsequent trials a strong modulation of d_y and concurrent modulation of

250   d_{LF} enabled T_{com} to return to pre-cTBS levels (Fig. 5B; *SI Appendix*, S6 and Fig. S3).

251

252   **Disruption of S1 impairs the modulation of load force distribution**

253   cTBS over S1 affected only digit load force distribution, d_{LF} being significantly reduced

254   relative to *Pre* block trials (main effect of *Block*: $F_{2,18}$ = 16.50, P < 0.0001, $\eta_p^2 = 0.65$;

255   post1 vs pre5: t_9 = −4.187, P = 0.002, Cohen's d_z = 1.32; Fig. 5A, S1 *uncon* column). In

256   contrast, F_{GF} and d_y were statistically indistinguishable from trials preceding cTBS (no

257   main effect of *Block*: $F_{2,18}$ = 0.867 and 2.34, respectively; both P > 0.13; both $\eta_p^2 < 0.2$;

258   Fig. 5A). Therefore, the reduction in d_{LF} was the primary cause of T_{com} reduction on the

259   first post-cTBS trial (Fig. 4A). Subsequent modulation of d_{LF} contributed the most to the

260   recovery of T_{com} to pre-cTBS levels (Fig. 5B; *SI Appendix*, S6 and Fig. S3).

261

262   **DISCUSSION**

263   Dexterous manipulation requires not only precise force application over time, but also

264   adjusting forces to where they are applied on an object. In most every day hand-object

265   interactions, digit contact points are not cued or constrained by an object's geometrical

266   features. Nevertheless, humans are exquisitely skilled at repeatedly manipulating an

267   object despite the fact that grasping may occur at different contact points on the object.

268   Such variability in digit placement persists even after the object's dynamic properties

269   have been learned (25). Digit position variability is compensated for by modulating digit

270   forces in an anticipatory fashion, i.e., before object lift-off (25, 26). This digit force-to-

271   position modulation is critically important for ensuring that manipulation goals are

272   accurately accomplished. This evidence points to the involvement of a feedback-based

273   control of digit forces. In this case, sensed digit placement would be used to modulate

274   digit forces accordingly on a trial-to-trial basis.

275   From a neural control perspective, we had proposed that constraining or allowing

276   choice of contact points challenges the nervous system in different ways (25–27, 30,

277   34). Constraining digit position enables the memory retrieval of grasp forces used in

278   previous manipulations. In contrast, the larger digit position variability when allowing

279   choice of contacts limits the extent to which subjects can use memory-based control of

280   forces. The present study tested whether digit force-to-position modulation is mediated

281   by differential activation and communication between sensorimotor cortices.

282   Our combined results across EEG and TMS studies revealed a differential

283   involvement of M1 and S1 in unconstrained relative to constrained grasping. While we

284   demonstrated that the neural activity of both M1 and S1 is greater in unconstrained

285   grasping, only the effective connectivity from S1 to M1 was affected by grasp context

286   (Fig. 3*C*). A series of TMS experiments further elucidated the functional roles of M1 and

287   S1. When digit position was constrained to be repeatable and predictable across trials,

288   we confirmed previous work pointing to the role of M1 in mediating a memory-based

289   control of manipulative forces (15, 17) and S1's lack of involvement in digit force retrieval

290   (31) (Fig. 5*A*, M1 *con* and S1 *con*). More importantly, for unconstrained grasping we

291   demonstrated that integrity of both M1 and S1 is critically important as they have

292   complementary roles in mediating digit force-to-position modulation (Fig. 5*A*, M1 *uncon*

293   and S1 *uncon*). Together, our results suggest that control of dexterous manipulation

294   relies on a flexible organization of the sensorimotor cortical network depending on

295   whether contact points can be chosen or not.

296

Effects of cTBS on grasp control variables are sensitive to grasp context

298   Previous work combining TMS-induced virtual lesions and a constrained grasping

299   task identified M1 as being implicated in storage and retrieval of sensorimotor memory of

300   grasp forces (15, 17, 35). Our results confirm such a role, while extending these

301   observations in important ways. Specifically, when contact points were predictable,

302   virtual lesions to M1, but not S1, prevented retrieval of learned digit forces (M1 and S1

303   *con*, Fig. 5*A*). In contrast, when contact points were not as predictable as in constrained

304   grasping, virtual lesions to M1 elicited two inter-related phenomena: subjects could not

305   implement digit placement similar to that before delivery of cTBS, and digit forces were

306   not modulated as a function of the new digit placement (M1 *uncon*, Fig. 5*A*).

307   Furthermore, cTBS to S1 impaired digit force-to-position modulation (M1 *uncon*, Fig.

308   5*A*). Thus, in both *uncon* groups, cTBS impaired the critical ability to modulate digit

309   forces to position, but did so by selectively affecting different T_{com} variables.

310   Analysis of the time course of cTBS effects beyond the first post-cTBS trial provided

311   additional insights. Specifically, when digit force control was predominantly driven by

312   sensorimotor memory, the M1 *con* group's inability to retrieve digit forces and restore

313   pre-cTBS T_{com} persisted for all post-cTBS trials (Fig. 5*B*). In contrast, for the S1 *con*

314   group the small (non-significant) effect of cTBS on d_Y (Fig. 5*A*) and T_{com} reduction

315   disappeared after the first post-cTBS trial due to small changes in digit centers of

316   pressure (Fig. 5*B*; *SI Appendix,* S6 and Fig. 3S). Importantly, the M1 and S1 *uncon*

317   groups were able to restore digit force-to-position modulation and T_{com} within the first

318   five post-cTBS trials.

319   The different time courses of post-cTBS recovery in each T_{com} variable further

320   indicates differences in the roles of M1 and S1 according to the grasp context. The most

321   striking difference was found in the timeline of post-CTBS effects across M1 and S1 *con*

322   groups, i.e., F_{GF} and d_{LF} were affected for 15 trials, whereas the small effect on d_Y

323   lasted 1 trial, respectively (Fig. 5*B; SI Appendix,* S6 and Fig. 3S). These findings confirm

324   M1 – but not S1 – is involved in storing or retrieving memory of digit forces. As cTBS to

325   S1 did not affect digit forces, the quick recovery of d_Y through small changes in digit

326   position in the S1 *con* group could have been driven by visual feedback of object roll

327   caused by the sudden T_{com} reduction on the first post-cTBS trial (Fig. 4*A*,*B*). These

328   results suggest that the memory-based force control mechanism affected by cTBS

329   cannot benefit from visual feedback of manipulation error to the same extent as digit

330   placement, even when such errors continue to occur across multiple trials.

331   With regard to the *uncon* groups, cTBS to M1 and S1 again affected different T_{com}

332   variables, i.e., d_Y and d_{LF}, respectively (Fig. 5*A*). Importantly, both groups were able to

333   restore pre-cTBS T_{com} by re-establishing digit force-to-position modulation, but did so in

334   different ways. Specifically, the M1 *uncon* group modulated both d_Y and d_{LF}, whereas

335   the S1 *uncon* group modulated only d_{LF} (Fig. 5*B; SI Appendix,* S6 and Fig. 3S). These

336   differences in short- and long-term effects of cTBS, as well as the T_{com} variables affected

337   by the virtual lesion, underscore the complementary, yet different roles of M1 and S1 in

338   unconstrained grasping. Specifically, integrity of both M1 and S1 is needed to modulate

339   digit force to position, even though a virtual lesion to either area can be compensated by

340   the other. Similar to the recovery of pre-cTBS levels of T_{com} proposed for the *con* groups,

341　we speculate that this recovery in the *uncon* groups was also mediated by visual

342　feedback of object roll, as well as digit placement which could be changed in a trial-to-

343　trial basis.

344　　　The above results contribute to extant evidence indicating M1 is largely involved with

345　motor memory processes. For example, previous studies have shown that

346　neurostimulation to M1 during motor learning tasks affects recall but not the learning

347　process itself (36, 37). Importantly, in unconstrained grasping cTBS to M1 disrupted digit

348　force modulation to position, while leading participants to rely on memory of forces (Fig.

349　5*A*). These findings indicate the role of M1 is not limited to a memory-based control

350　process: it is also directly involved in using trial-by-trial sensory feedback of digit position

351　to scale forces.

352　　　Our focus on S1 was motivated by a long history of research on the role of S1 in the

353　context of online feedback control (e.g., (38–40)). While it is clear that S1 provides

354　proprioceptive inputs to M1 (41–44), what remains unclear is whether this process is

355　context dependent. We hypothesized that increased communication of proprioceptive

356　inputs from S1 to M1 would be necessary in unconstrained grasping. Our cTBS results

357　support this prediction by showing an impaired ability to adjust forces online to position.

358　This suggests that S1 cTBS inhibited communication to M1 and supports S1 has a

359　context-dependent role. Recent evidence further supports this proposition by indicating

360　that S1 is also involved in motor learning (45). These authors demonstrated that

361　optogenetically silencing S1 during motor adaptation inhibited learning. The implication

362　of this finding and our S1 cTBS results is that somatosensory cortex plays a critical role

363　in providing feedback information for both online control and learning.

364

365　**M1-S1 communication specificity across grasp contexts**

366　The cTBS results highlight the individual roles of M1 and S1 as a function of grasp

367　context. Nonetheless, they clearly show that their functional roles are not independent.

368　Our framework predicted S1 would increases communication of proprioceptive inputs to

369　M1 in unconstrained grasping. We used EEG connectivity analysis to test this

370　hypothesis. Specifically, we anticipated a two-way interaction between grasp context and

371　the extent to which S1 drove activity in M1, and vice versa. Our analysis confirmed this

372　prediction that connectivity from S1 to M1 was increased in unconstrained grasping (Fig.

373　3*B*,*C*). Accordingly, greater connectivity from S1 to M1 in unconstrained grasping and

374　the behavioral effect of S1 disruption are consistent with the proposition that S1 would

375   provide M1 with feedback of digit position. This raises an auxiliary but important question

376   of which brain area may set the context-dependency. Previous work on M1-S1

377   interactions in rats concluded that M1 may cue S1 to gate thalamic inputs in response to

378   whisker stimulation (46). We found that M1 to S1 connectivity was similar across grasp

379   contexts, suggesting that the control of sensory gating may also be driven by S1.

380   Beyond connectivity, an imperative question is whether local activity in M1 and S1

381   was also context dependent. When examining power, we focused our analysis on 9-12

382   Hz (alpha). We chose this frequency band because substantial support has been

383   provided for its association with cortical inhibition within sensory cortices (47). Unlike the

384   connectivity results, we found that power increased in both M1 and S1 in unconstrained

385   grasping. We suggest that the increase in power likely represents an increase in local

386   inhibition across both areas to gate inputs from external sources (48, 49). This overall

387   increase in power, combined with the connectivity result, indicate that both local

388   inhibition and inter-areal communication may instatiate distinct processes during

389   feedback-driven sensorimotor control.

390

391   **Primacy of contact event for somatosensory feedback**

392   We should note that S1's role in processing sensory inputs associated with digit

393   position is not obligatory. Conceptually, force planning could arise prior to contact, when

394   the digits are visible. While such vision-based force planning is still possible, contact

395   detection through visual, proprioceptive, and tactile feedback has been shown to be a

396   critical event for signaling the transition from the end of hand transport and onset of force

397   application (for review see 11). We propose that feedback during object contact is also

398   instrumental for estimating the relative position of the digits. Importantly, the S1 *uncon*

399   results indicate that visual feedback of the hand trajectory and contact points – available

400   throughout the task – could not compensate for the effect of the virtual lesion on digit

401   force-to-position modulation. The notion that object contact is the most relevant event for

402   feedback processing in unconstrained grasping is supported by a recent study showing

403   significant grasp-context differences in corticospinal excitability at contact, but not during

404   the reach (30). In summary, our findings support the imperative role of somatosensory

405   feedback of digit position for digit force modulation at object contact, but not during

406   reaching.

407

408   **Grasp cortical network for constrained and unconstrained grasping**

409   It is well known that the cortical network underlying grasp control, which has been

410   defined primarily based on research on constrained grasping, comprises several areas.

411   For example, the anterior region of intraparietal sulcus (aIPS) and premotor ventral

412   (PMv) contribute to accurate hand shaping prior to object contact (8), whereas aIPS,

413   premotor dorsal area (PMd), and M1 are involved in the storage and/or retrieval of force

414   scaling appropriate for the hand shape used in the grasp (50). Studies in patients with

415   posterior parietal cortex lesions revealed that they experience difficulties in shaping the

416   fingers according to intrinsic object features (51) and impaired predictive scaling of grip

417   forces during self-induced modulation of load forces (52). In neurologically-intact

418   individuals, TMS-induced disruption of PMv and bilateral aIPS areas prior to object lift-off

419   leads to increased variability in hand shaping (14, 53–55), whereas TMS disruption of

420   contralateral aIPS, PMd and M1 results in inaccurate grip force and load force scaling

421   (14, 15). S1 appears to be involved in sensing of predictable (31) and unpredictable (17)

422   contact events occurring at the fingertips during constrained grasping. In sum, when

423   contact points are constrained, dexterous manipulation relies on interactions among

424   posterior parietal areas, such as aIPS and S1, and frontal areas such as PMv, PMd, and

425   M1 (56, 57).

426   Besides the above-cited study on corticospinal excitability (30), to the best of our

427   knowledge only one study examined the extent to which control of constrained and

428   unconstrained grasping is mediated by different brain areas (29). The main findings of

429   this fMRI study were that cerebellum, BA 44, and PMv were differentially activated

430   across the two grasp contexts. However, in contrast to our EEG and cTBS results, no

431   differences were found in M1 and S1 activity. A direct comparison between these studies

432   is not possible due to several methodological differences, i.e., in the fMRI study T_{com}

433   variables could not be measured in the scanner and subjects were instructed to

434   deliberately vary digit position across trials in the unconstrained condition. Nevertheless,

435   in the present study our cTBS results identified a causal and grasp context-dependent

436   role of M1 and S1, which is consistent with the EEG results of greater S1-M1 effective

437   connectivity. Future studies are needed to extend these observations to other brain

438   areas of the grasp network.

439

440   **Revised conceptual framework of neural control of manipulation**

441   The present findings significantly extend our understanding of neural mechanisms

442   underlying dexterous manipulation. Specifically, they reveal that the neural and control

443   mechanisms are differentiated between constrained and unconstrained grasping, the

444   latter mimicking more natural conditions. These findings necessitate a revision to current

445   frameworks explaining dexterous manipulation. We used the current and previous

446   results to provide the foundation for a revised theoretical framework (Fig. 6).

447   It has been established that interactions between M1, sensory, as well as premotor

448   and parietal cortical areas, lead to hand shaping (58, 59), which culminates with

449   positioning the digits at remembered locations used in previous manipulations.

450   Somatosensory and visual inputs contribute to guiding the hand towards the planned

451   contact points on the object (Fig. 6).

452   Our theory posits that following object contact, subjects use feedback of digit position

453   to determine the similarity of contact points with those used in previous manipulations.

454   We propose that sensing digit position serves a dual role. The first and obvious role is

455   detecting the digit contact points. However, the utility of this is driven by whether these

456   contact points were constrained or unconstrained, necessitating a second role. For

457   constrained grasping, this role is minimally important beyond ensuring force control that

458   satisfies mechanical requirements, i.e., normal-to-load force modulation (33, 60). In

459   contrast, during unconstrained grasping we propose that manipulation is predominantly

460   driven by a mechanism that compares predicted and actual sensory feedback of digit

461   position (Fig. 6). We anticipate that individuals use this mechanism to determine the

462   extent to which force control is driven by memory and online feedback. The relative

463   contribution of each mechanisms depends on the extent to which predicted and actual

464   contact points match. Daily grasping activities, e.g., unconstrained grasping, elicit

465   greater reliance on feedback because of the inherent variability of contact points.

466   Our work underscores the context-dependent roles of M1 and S1 for the control of

467   dexterous object manipulation by revealing the dual role of M1 and its synergistic

468   interactions with S1 for the trial-to-trial modulation of digit force to position. Importantly,

469   adding one degree of freedom (choice of digit position) to the control space of

470   manipulation elicited *different* roles of M1 and S1 to perform the *same* task. Specifically,

471   as the number of solutions (force-position relations) increases, the communication

472   between M1 and S1 becomes more critical. Future work should examine the contribution

473   of higher-order frontal and parietal cortical areas to building high-level task

474   representations required to drive the coordination of digit position and forces to attain a

475   given task goal, i.e., preventing the object from slipping or tilting during manipulation.

476

477 **MATERIALS AND METHODS**

478

479 **Subjects**

480 One hundred naïve right-handed volunteers (23 ±4.12 years [mean ± SD]; 44 females)

481 with normal or corrected-to-normal vision and no history of musculoskeletal disorders or

482 neurological disease participated in this study. Subjects were screened for potential risks

483 of adverse reactions to transcranial magnetic stimulation (TMS) using the Transcranial

484 Magnetic Stimulation Adult Safety Screen (61) and gave their written informed consent

485 according to the declaration of Helsinki. All protocols were approved by the institutional

486 review boards at Arizona State University and the University of Houston.

487

488 **Grip device**

489 A custom-designed inverted T-shaped object instrumented with two six-dimensional

490 force and torque transducers (Nano 25; ATI Industrial Automation, Garner, NC) (Fig. 1*A*)

491 was used to record forces and torques exerted by the index fingertip and thumb.

492 Graspable surfaces (sandpaper, grit #320) consisted of two long parallel PVC plates

493 (140 × 22 mm), each mounted vertically on one transducer (Fig. 1*A*). The grip device

494 measured grip and load force (normal and tangential/vertical to the graspable surface),

495 and each digit's center of pressure. The transducers' location relative to the graspable

496 surfaces was blocked from the subject's view to prevent visual cues from biasing the

497 choice of digit placement. A 400-g mass was placed in the right (relative to the subject)

498 compartment at the base of the grip device and was hidden from view to prevent

499 subjects from anticipating the object's mass distribution. The added mass created an

500 external torque in the frontal *x-y* plane of 255 N•mm (T_{ext}, Fig. 1*A*). The object's total

501 mass was 790 g. Each end of the object's base was placed on a lift switch. The release

502 of either switch by upward movement of the object from the table signaled object lift

503 onset. We used a wireless inertial measurement unit (IMU, Emerald, APDM, Portland,

504 OR) fastened to the top of the object to measure object tilt during the lifting phase.

505

506 **Experimental Protocol**

507 Subjects sat comfortably in a custom TMS chair (Rogue Research Inc., Canada),

508 with right hand pronated and resting on a hand switch. Subjects were asked to reach

509 and grasp the grip device placed on a table 15 cm in front of them using the thumb and

510 index fingertip at a self-selected speed, lift the object vertically to a height of 5–10 cm

511   above the table, hold the object for 2–3 seconds, replace the object on the table, and

512   return their hand to the hand switch until the next trial. During each trial, subjects were

513   asked to lift the object as straight as possible, i.e., to prevent the object from rotating on

514   the frontal plane due to the right-sided asymmetrical mass distribution (Fig. 1*A*).

515   Successful performance required subjects to exert a compensatory torque (T_{com}) of the

516   same magnitude but in the opposite direction of T_{ext} in an anticipatory fashion, i.e., at

517   object lift onset (25). The rationale for the task design is described in S1 (*SI Appendix*).

518   Subjects were asked to perform our manipulation task by either allowing them to

519   choose grasp contact locations (unconstrained grasping, *uncon*) or constraining contact

520   locations by visually cueing grasp points on the object (constrained grasping, *con*) (top

521   and bottom objects, respectively, in Fig. 1*A*). The functional roles of M1 and S1

522   underlying control of *con* and *uncon* grasping were investigated in two separate

523   experiments using electroencephalography (EEG) or transcranial magnetic stimulation

524   (TMS).

525   For the *uncon* grasping condition in both EEG and TMS experiments, subjects were

526   instructed that they could grasp anywhere along the vertical plates to perform the task.

527   For the *con* grasping condition in the EEG experiment, the contact point of each digit

528   was visually cued using two LEDs (vertical distance: 14 mm) on each side of the object

529   within which the fingertip had to be placed. The EEG study addressed differences in

530   source activation of primary motor and sensory cortices (M1 and S1, respectively) and

531   their effective connectivity during execution of *con* versus *uncon* grasping. We expected

532   these differences to reflect a greater involvement of feedback- vs. memory-based control

533   of forces in *uncon* than in *con* grasping (27). We asked subjects to perform a learning

534   block of 10 *uncon* trials (Fig. 2*A*). As the largest performance improvements (i.e.,

535   minimization of peak object roll) occurs within the first three trials (25, 26), we used the

536   mean of subjects' preferred digit placement at object lift onset in trials 6-10 of this

537   learning block to set the location of the LED boundary locations for the *con* context. This

538   procedure ensured that average digit position and force distributions would be

539   statistically indistinguishable across *con* and *uncon* trials, while leaving intact the trial-to-

540   trial force position modulation which only occurs in the *uncon* grasping condition. Thus,

541   EEG activation differences that might occur when comparing *con* versus *uncon* grasping

542   conditions would only be attributable to processes associated with digit force-to-position

543   modulation occurring between contact and object lift-onset in the *uncon* grasping

544   condition. After the learning block, subjects performed 60 experimental trials that were

545   used for EEG analysis. Specifically, half of the subjects performed a block of 30 *uncon*

546   trials followed by a block of 30 *con* trials, whereas the other half performed these two

547   blocks of trials in the opposite order (Fig. 2*A*). This design controlled for potential order

548   effects of block presentation. Statistical analysis confirmed lack of significant differences

549   in T_{com} and related variables (see equation 1) within each grasping condition regardless

550   of the order of presentation.

551   Unlike the EEG study, the *con* grasping condition in the TMS experiment was

552   designed to address the question of whether the control of digit force and position

553   differed following a virtual lesion to M1 (Fig. 2*B*). Specifically, the pre- versus post-TMS

554   comparison was performed within each grasping condition, and therefore did not require

555   to statistically match digit force and position at object lift onset across *con* and *uncon*

556   grasping conditions. To allow comparison with previous studies of *con* grasping, subjects

557   were instructed to grip the object at fixed collinear locations indicated by a horizontal

558   marker placed across the front of the object (vertical length: 20 mm; see Fig. 1*A*). For

559   both *uncon* and *con* grasping conditions, a computer monitor placed behind the object

560   presented two visual cues to the subject to guide each trial. The first 'ready' cue signaled

561   the beginning of a trial, and after a random delay (1-3 s) subjects were shown a 'go' cue

562   to initiate the reach. To allow subjects to learn the dynamics of the object, they were

563   asked to perform 10 practice trials ("*Learn*" block) (Fig. 2*B*). Following this block,

564   subjects then performed two blocks (*"Pre"* block, *"Post"* block) of 15 trials each. TMS

565   was delivered between the *Pre* and *Post* block (see below). Each block was separated

566   by a rest time of 5 minutes (Fig. 2*B*).

567

568   **Electroencephalography: Procedures**

569   EEG was recorded from 22 subjects using a 64-channel Acticap system

570   (BrainVision, Morrisville, NC) at a sampling rate of 1 kHz, with resolution 0.1 µV and

571   bandpass filter of 0.1-100 Hz, and impedances kept < 10kΩ. 3-D electrode locations

572   were recorded using a Captrak camera system (BrainVision, Morrisville, NC). EEGLAB

573   was used to perform EEG pre-processing steps (62). Continuous data were first high-

574   pass filtered (0.5 Hz). Eye movement and blink artifacts were removed using

575   Independent Components Analysis (Extended INFOMAX algorithm)(63). On average,

576   4.46 (± 3.33) components were removed per participant. General EEG procedures are

577   described in S2 (*SI Appendix*).

578

Transcranial magnetic stimulation: Procedures

579

580   We delivered single-pulse TMS (spTMS) to primary motor cortex (M1) of 78 subjects

581   using a Rapid[2] stimulator (Magstim, 70-mm figure-of-eight coil, Whitland, UK).

582   Suprathreshold TMS pulses delivered over contralateral (left) M1 representing the right

583   first dorsal interosseus muscle (FDI) were used to estimate resting motor threshold

584   (rMT) (64). To assess corticospinal excitability (CSE), we delivered spTMS with the

585   intensity set at 120% of rMT over the identified FDI region.

586   We delivered continuous theta burst stimulation (cTBS) to M1 and S1 at an intensity

587   of 80% of active motor threshold (aMT) (65) to transiently disrupt neural activity.

588   Repetitive pulses were delivered in the form of 3 pulses at 50 Hz repeated every 200 ms

589   for 40 s (600 pulses) (65, 66). As cTBS over M1 has been shown to decrease the size of

590   MEPs, we measured CSE using spTMS to verify the effects of cTBS over M1 (66) and

591   S1 (67).

592   For M1 cTBS, the TMS coil was positioned over the left cerebral hemisphere

593   representing the right FDI muscle, as identified during rMT estimation. For S1 cTBS, we

594   positioned the TMS coil over the postcentral gyrus posterior to the M1 FDI hotspot (68).

595   To locate the stimulation site, we used high-resolution T1-weighted MRI scan (3T Philips

596   Ingenia scanner) obtained from each subject and used it to reconstruct a three-

597   dimensional brain to display the cortical surface (Brainsight software, Rogue Research

598   Inc., Canada) (65). The mean Montreal Neurological Institute coordinates of the

599   stimulation sites for left S1 were -41.75 ±10.37, –25.27 ±15.21, 57.11 ±5.47 (x, y, z,

600   mean ±SD; *n* = 20). For vertex stimulation (see below), the TMS coil was positioned over

601   Cz, based on the 10-20 international system (69) with the TMS handle oriented

602   posteriorly in alignment with the interhemispheric fissure (70). The coil position for S1

603   and vertex was confirmed by the delivery of single TMS pulses at 120% of rMT to ensure

604   that there were no MEPs in the FDI muscle. General TMS procedures are described in

605   S2 (*SI Appendix*).

606

607   **TMS experiment: Experimental Groups**

608   We delivered cTBS to four groups of subjects (Fig. 2*B*). We stimulated M1 and S1 of

609   subjects performing the *con* and *uncon* grasping condition (*M1 con,* S1 *con,* M1 *uncon*,

610   and S1 *uncon*; *n* = 10 in each group). cTBS was delivered between the *Pre* and *Post*

611   blocks. CSE was assessed using spTMS immediately before and 5 minutes after cTBS

612   (66) (Fig. 2*B*).

613

614 **TMS Experiment: Control Groups**

615 We performed five control experiments to assess the specificity of cTBS effects over M1

616 and S1 and the efficacy of the cTBS protocol: *Vertex* (*n* = 10), *Sham* (*n* = 10), *No cTBS*

617 (*n* = 6), *No Stim* (*n* = 6), and *No Move* (*n* = 6). All control groups, with the exception of

618 the *No Move* group, performed the manipulation task in the *uncon* grasping condition

619 (Fig. 2*B*). Unless otherwise stated, cTBS occurred between the *Pre* and *Post* blocks,

620 and CSE was assessed over contralateral (left) M1 region immediately after the *Pre*

621 block and before the *Post* block (Fig. 2*B*).

622 In the *Vertex* group, cTBS was delivered over vertex to assess specificity of cTBS-

623 induced effects observed in the M1 and S1 groups (65, 71).

624 In the *Sham* group, cTBS was delivered using a second coil placed directly behind

625 the TMS chair's headrest with current directed away from the scalp while the coil over

626 contralateral (left) M1 remained in place. This group was used to control for any

627 somatosensory effects caused by the auditory cue of cTBS on the control of object

628 manipulation (72).

629 For the *No cTBS* group, no cTBS stimulation was used. This served to quantify the

630 potential effects of MEP-induced movements on manipulation performance, as these

631 muscle twitches have been shown to affect grasping behavior (35).

632 Subjects in the *No Move* group received cTBS over contralateral M1, and saw the

633 same visual cues as those presented to all other groups. However, they were asked to

634 remain at rest when seeing the 'go' cue rather than performing the motor task. This

635 control group was used to validate the effects of cTBS over M1 on MEP size using the

636 protocol that has been previously reported in the literature (66).

637 Subjects in the *No Stim* group received neither spTMS nor cTBS (Fig. 2*B*). This

638 group was used to control for any somatosensory effects caused spTMS and cTBS on

639 the control of object manipulation (72).

640 For additional details and rationale for the control conditions, please refer to

641 *SI Appendix*, S5.

642

643 **EEG data analysis**

644 Dipole moments (pA*m) were used to quantify neural activity in the alpha band (9-12

645 Hz). Source maps were projected to a default brain (73) and subsequently decibel-

646 normalized to a baseline period (average of −500 to −250 ms before a 'ready' cue) (Fig.

647   3A). After baseline normalization, data recorded between contact and object lift onset

648   were averaged within subjects for each condition prior to statistical analysis. Source

649   localization and analysis was performed using a combination of the Brainstorm toolbox

650   (74) and Brainsuite (75) for cortical parcellation of individual subject structural T1-

651   weighted MRIs (3T, Philips). The cortical surfaces for each subject were reconstructed

652   from the MRIs using Brainsuite. MRIs were co-registered with EEG electrode locations,

653   and used to create a boundary element model (BEM) of scalp, outer skull, and inner

654   skull before source estimation. Source cortical activity from each trial was estimated

655   using distributed source imaging based on a depth-weighted (L2 Norm) minimum-norm

656   estimation (MNE) that estimated an orientation constrained dipole at each parcellated

657   location from the BEM (total of 15,000 dipoles) (76) and converted to current density

658   maps (77). Our subsequent analysis focused on two regions of interest (ROI): left

659   precentral and postcentral gyrus, corresponding to M1 and S1, respectively. These ROIs

660   were identified through automatic neuroanatomical labeling in Brainsuite (Fig. 3A).

661

662   **TMS data analysis**

663   Electromyography (EMG) signals were recorded from the right FDI muscle using bipolar

664   surface electrodes (Delsys Bagnoli system, Boston, MA) and digitized at 5 kHz (Power

665   1401 Cambridge Electronic Design, Cambridge, UK). Peak-to-peak MEP amplitudes

666   (mV) were measured and extracted using a custom written Spike2 script and analyzed

667   using Matlab. EMG signals were screened online and recorded during cTBS stimulation

668   to verify that cTBS did not evoke MEPs.

669

670   **Behavioral data analysis**

671   Data from force/torque sensors and the IMU gyroscope (range of ±2000°/s and noise

672   density of 0.05 rad/s/√Hz) were sampled at 1000 Hz and 128 Hz, respectively. Force,

673   torque, and object roll data were used to compute the following variables (Mathworks,

674   Natick, MA): (1) *Digit forces*: Digit tangential force (F_{tan}) is the vertical force component

675   parallel to the grip surface produced by each digit to lift the object (Fig. 1A,B). Digit load

676   force data exerted by each digit was used to compute the difference between thumb and

677   index finger load forces ($F_{tan1} - F_{tan2} = d_{LF}$). Digit normal force ($F_n$) is the force

678   component normal to the grip surface produced by each digit (Fig. 1A,B). Digit grip force

679   was defined as the average of the thumb and index finger normal forces ([$F_{n1} + F_{n2}$]/2 =

680   F_{GF}). (2) *Digit center of pressure*: The center of pressure of thumb and index fingertip

681 (CoP$_1$ and CoP$_1$, respectively) was computed using the force and torque output of each

682 sensor (25) (Fig. 1A,B). CoP data were then used to compute the vertical distance

683 between the CoP on the thumb and finger side of the grip device (CoP$_1$ – CoP$_2$ = d$_Y$).

684 We computed the compensatory torque exerted on the object (T$_{com}$, Fig. 1A,B) using the

685 following equation:

$$T_{com} = d_{LF} \cdot \frac{w}{2} + d_Y \cdot F_{GF} \qquad (1)$$

687 where 'w' denotes the width of the object. (3) *Peak object roll*: Our previous studies have

688 demonstrated that T$_{com}$ is a valid predictor of manipulation performance, i.e., object roll.

689 Specifically, as subjects learn the appropriate T$_{com}$ required to minimize object roll, peak

690 object roll negatively correlates with the magnitude of T$_{com}$ (25, 26, 31, 63). This was

691 confirmed by a significant linear correlation between T$_{com}$ and peak object roll (Pearson

692 correlation coefficient on data pooled across all experimental groups and subjects: 0.68;

693 $P < 0.001$). We also note that the results of the analysis of peak object roll and T$_{com}$ were

694 identical across all experimental and control groups.Therefore, as both variables capture

695 two interrelated phenomena associated with learning dexterous manipulation, for the

696 sake of brevity we report only results of the analysis of T$_{com}$.

697 All of the above variables were computed at the time of object lift onset to quantify

698 anticipatory control of manipulation (24, 25). Object lift onset was defined as the time at

699 which the first of the two object switches was released from the object switch plate and

700 remained open for 50 ms.

701

702 **Statistical analysis**

703 *EEG experiment.* Baseline normalized dipole moments averaged within subjects for

704 each grasping condition (30 trials each; Fig. 2A) were compared using t-tests with

705 Bonferroni corrections. Our framework predicts that the neural drive from S1 to M1

706 should be greater for *uncon* compared to *con* grasping between contact and object lift

707 onset. To this end, we used Granger causal (GC) analysis on the M1 and S1 source-

708 reconstructed EEG data to determine the effective connectivity between these regions.

709 The time epochs used to analyze these data were pulled from the same time window

710 used to analyze source power. For each grasp context, the GC values between M1 and

711 S1 were estimated using all trials for each subject individually. By analyzing all trials at

712 the same time for a given subject and condition, we were able to determine whether

713 there was an overall significant effective drive between M1 and S1 (and vice versa) in a

714 subject- and condition-specific manner. GC was estimated using the Matlab MVGC

715   toolbox (79). The toolbox fits multivariate vector autoregressive models up to a certain

716   delay order. This model was estimated on a subject and condition basis to optimize the

717   model fit. We detected significant GC in all subjects and conditions, all of which were

718   used for analysis in a repeated measures ANOVA.

719   *TMS experiment.* We assessed subjects' ability to perform the manipulation task by

720   comparing T_{com} from the first trial with the average of the last five trials of each block

721   (*Learn, Pre, Post*) within and across experimental groups (Fig. 2*B*). Our previous work

722   has shown that subjects quickly learn to generate the necessary T_{com} (Fig. 4) within the

723   first three trials so as to minimize object roll (25, 80). Analysis of the first trial of each

724   block thus allowed the assessment of subjects' performance without any previous

725   experience (*learn1*), and recall of stored sensorimotor memory of grasp position and

726   forces acquired after learning the manipulation task (*pre1, post1*). Subsequently,

727   averaging the last five trials of each block (*learn5, pre5, post5*) was performed to obtain

728   a measure of stability of performance for each block.

729   To assess learning-related changes in T_{com}, we performed a 5 x 2 between-within

730   repeated measures (rm) ANOVA with *Group* (5 levels: M1 *uncon*, M1 *con*, S1 *uncon,* S1

731   *con*, Vertex) as the between-subject factor, and *Block* (2 levels: l*earn1*, *learn5*) as the

732   within-subject factor. To confirm that subjects' performance remained stable during trials

733   after learning and prior to cTBS, we performed a 5 x 3 between-within rmANOVA with

734   *Group* as the between-subject factor, and *Block* (3 levels: *learn5*, *pre1*, *pre5*) as the

735   within-subject factor. A similar statistical design was used to assess T_{com} in the

736   remaining control groups (for details see S2 and S5, *SI Appendix).*

737   To assess the effects of cTBS on T_{com}, we performed a 5 x 3 between-within

738   rmANOVA with *Group* as the between-subject factor, and *Block* (3 levels: *pre5*, *post1*,

739   *post5*) as the within-subject factor. Post-hoc t-tests and one-way ANOVAs were used to

740   compare between- and within-group differences, respectively. We performed separate

741   one-way rmANOVA to assess the effects of cTBS on individual T_{com} components (d_{LF},

742   d_y, and F_{GF}). We chose to perform only within-group analyses for individual position and

743   force data because subjects could have selected different magnitude of the of T_{com}

744   components giving rise to spurious between-group differences, even though the overall

745   goal of T_{com} generation is the same. Finally, we used one-sample t-tests on the

746   percentage changes (post- versus pre-cTBS, or following rest for the *No Move* group; *SI*

747   *Appendix,* Fig. S1) in MEP data. We applied Huynh-Feldt corrections when sphericity

748   assumption was violated. We used Dunnett's post hoc test to compare each

749 experimental group with the control group (i.e., Vertex). We used Bonferroni t-test for

750 posthoc comparisons between experimental groups. For within-subject factors, we

751 performed post hoc comparisons using paired t-tests with appropriate Bonferroni

752 corrections.

753   Our analysis examining the difference in T_{com} of *pre5* and *post1* trials allowed us to

754 quantify the immediate effect of cTBS to different neural sites. This revealed differential

755 changes in T_{com} components (Fig. 5*A*,*B*). To understand whether these effects persisted

756 or changed during the 15 post-cTBS trials, we calculated the difference of each post-

757 cTBS trial and *pre5* data to create a time series of values. We notate these values with a

758 Δ to represent the difference; for example, the difference in d_Y pre- versus post-cTBS is

759 denoted as Δd_Y (*SI Appendix,* Fig. S3). To analyze the potential changes in these

760 components as a function of *Group* over the time-course of *post-cTBS Trials* (1:15), $\Delta d_{Lf,}$

761 ΔF_{GF}, and Δd_Y were analyzed using a repeated-measures mixed-model framework.

762 *Group* entered the model as a between-subjects categorical factor, and *post-cTBS Trials*

763 entered as a continuous covariate. Because we anticipated time-based effects due to

764 the sequential nature of the task, we set the residual-covariance matrix to be scaled

765 within subject and have an autoregressive (lag-1) structure. The model was also set to

766 include random-intercepts for individual subjects. Each model was fitted using restricted

767 maximum likelihood, and always started with a full structure with both the effects and

768 interaction of *Group* and *post-cTBS Trial*. This full model was compared to each of the

769 simpler, nested models of just the effects using a likelihood ratio test to determine the

770 appropriate model. The final, reduced model is presented in S5, *SI Appendix*. All of the

771 analyses were computed in the R environment using the lme4 (81) and lmerTest (82)

772 packages.

773

774 **Contributions**

775 All authors contributed to the design of the study, data analysis and interpretation, and

776 manuscript preparation. PJP performed the TMS experiments, and JMF performed the

777 EEG experiments. All authors approved the final version of the manuscript.

778

779 **Competing financial interests**

780 The authors declare no competing financial interests.

781

782 **Acknowledgments**

792

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1017   **FIGURE CAPTIONS**

1018

1019   **Fig. 1** Grip device, experimental conditions, and experimental variables. (*A*) Schematic

1020   and free-body diagrams of the custom-built grip device for the unconstrained and

1021   constrained grasp conditions. (*B*) Experimental variables are shown for one representative

1022   trial of the manipulation task performed using an unconstrained grasp. From top to bottom,

1023   traces are thumb and index finger center of pressure (CoP), load and grip forces,

1024   compensatory and external torque (T_{com} , thick line, and T_{ext}, dotted horizontal line,

1025   respectively), and object roll (thin line). The sign of T_{com} has been inverted for graphical

1026   purposes. At object contact, the index finger is placed higher than the thumb and exerts

1027   larger load force. Nearly identical grip force is exerted by each digit. This subject generates

1028   a T_{com} that approaches T_{ext} at object lift onset, thus minimizing object roll (thin line; peak

1029   value < 5°). Vertical dashed lines from *left* to *right* denote reach onset, contact, and object

1030   lift off.

1031

1032   **Fig. 2** Experimental protocols. (*A*) For the electroencephalography (EEG) experiment, all

1033   subjects performed a block of 10 trials of the unconstrained grasp condition (*uncon*), after

1034   which they were split in two groups. One of these groups performed 30 trials of the

1035   constrained grasp condition (*con*) followed by 30 trials of the unconstrained grasp

1036   conditions, whereas the second group performed these grasp conditions in the opposite

1037   order. (*B*) In the transcranial magnetic stimulation (TMS) experiments, we delivered single

1038   pulse TMS and/or continuous theta burst stimulation (cTBS). The experimental groups (*n*

1039   = 4) performed our manipulation task in both *con* or *uncon* grasp conditions and received

1040   cTBS over M1 or S1. All control groups (*n* = 5), with the exception of "No Move", were

1041   tested in the *uncon* grasp condition. All groups, with the exception of "No Stim", received

1042   single pulse TMS before and after cTBS. All groups, with the exception of "No Move",

1043   performed 10 repetitions of the manipulation task during the Learn block and 15 repetitions

1044   each during the Pre- and Post-cTBS blocks.

1045

1046   **Fig. 3** EEG source current density power and effective connectivity. (*A*) Color-coded brain

1047   areas denote statistically significant source power differences (pA*m) between

1048   constrained and unconstrained grasping over left precentral and postcentral regions. (*B*)

1049   Mean normalized source power (decibel) for each grasp context. Overlaid gray lines show

1050   condition differences for individual subjects. ** denotes $P < 0.0125$. (*C*) Nodes showing
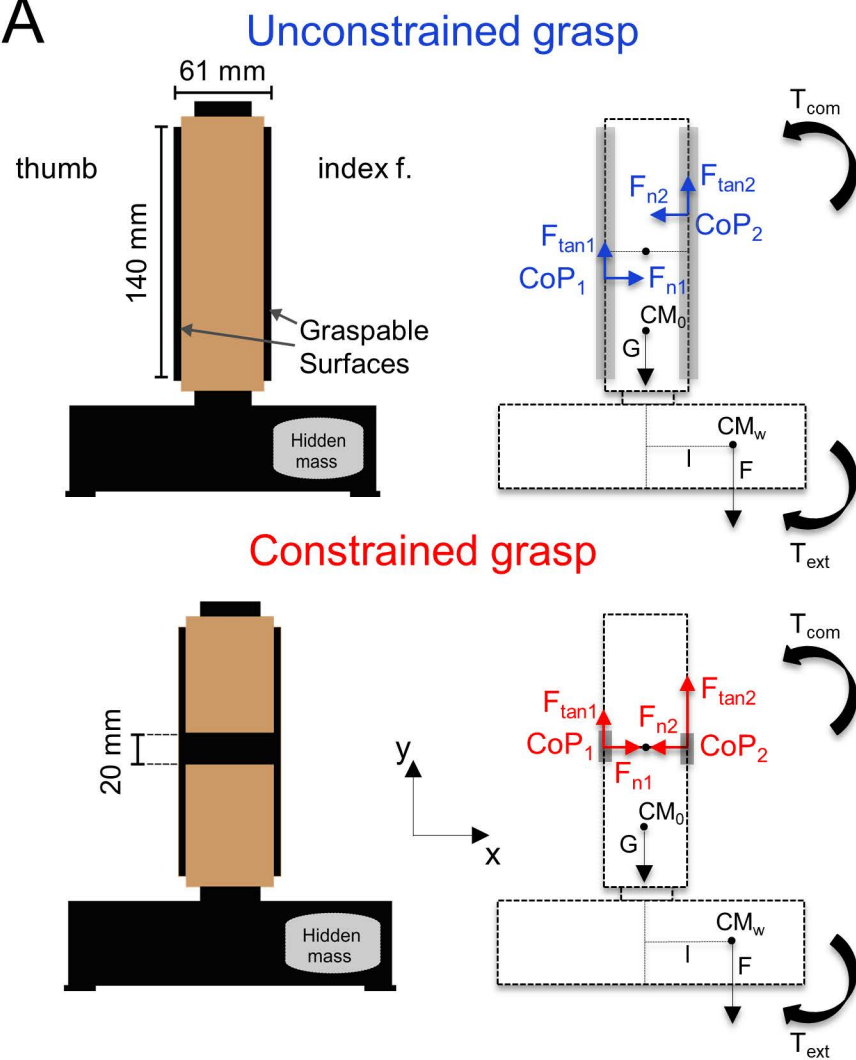
1051   the Granger causal values between M1 and S1 estimated from source reconstructed EEG

1052   data. The figure shows nodes for connectivity between M1 and S1 (pre- and post-central

1053   gyrus). The color of the arrow between nodes represents the strength of drive between

1054   areas. All connectivity values were significantly different than zero ($P < 0.05$). Data in *(A)-*

1055   *(C)* are from all subjects ($n = 22$) and were computed from object contact to lift.

1056

1057   **Fig. 4** Compensatory torque: Experimental groups and control condition (Vertex). (*A*)

1058   Compensatory torque (T_{com}) during the Learn, Pre, and Post blocks in the M1 *con*, M1

1059   *uncon*, S1 *con*, S1 *uncon*, and *Vertex* groups. The horizontal dashed line denotes the

1060   external torque induced by the added mass at the bottom of the object (T_{ext}) that should

1061   be compensated for by T_{com}. Shaded data denote trials used for plotting in *B* and analysis.

1062   (*B*) T_{com} on the first trial and the average of the last 5 trials for each block. ** denotes *P <*

1063   0.0125. Data are averages (± SE) of all subjects.

1064

1065   **Fig. 5** Effect of cTBS on digit load force, grip force, and position across all experimental

1066   conditions. (*A*) From top to bottom, traces denote time course of the difference between

1067   thumb and index finger load force (d_{LF}), grip force averaged across thumb and index finger

1068   (F_{GF}), and the vertical distance between thumb and index finger center of pressure (d_y)

1069   from contact ("0") to object lift onset. Data are averages of the last 5 trials prior to cTBS

1070   (Pre5) and first trial following cTBS (Post1). d_Y data are plotted from the time at which they

1071   can be accurately estimated using force and torque sensors (25). Data from each

1072   experimental group are shown across columns. Shaded plots denote T_{com} variables that

1073   were significantly affected by cTBS. (*B*) Data from Pre5 and each post-cTBS trial are

1074   shown for each T_{com} variable and experimental group. ** denotes $P < 0.0125$. Data are

1075   averages (± SE) of all subjects.

1076

1077   **Fig. 6** Cortical sensorimotor mechanisms for neural control of dexterous manipulation.

1078   The diagram shows a revised model describing the roles of M1 and S1 for the control of

1079   dexterous manipulation for constrained and unconstrained grasping contexts.
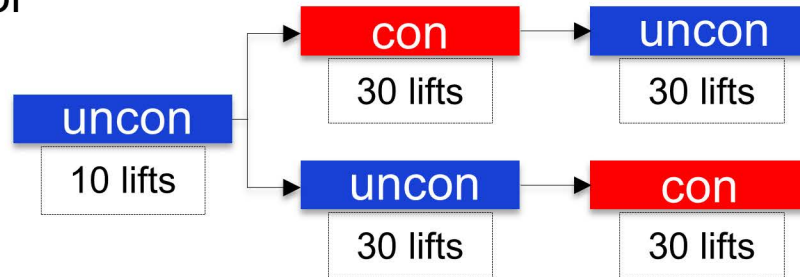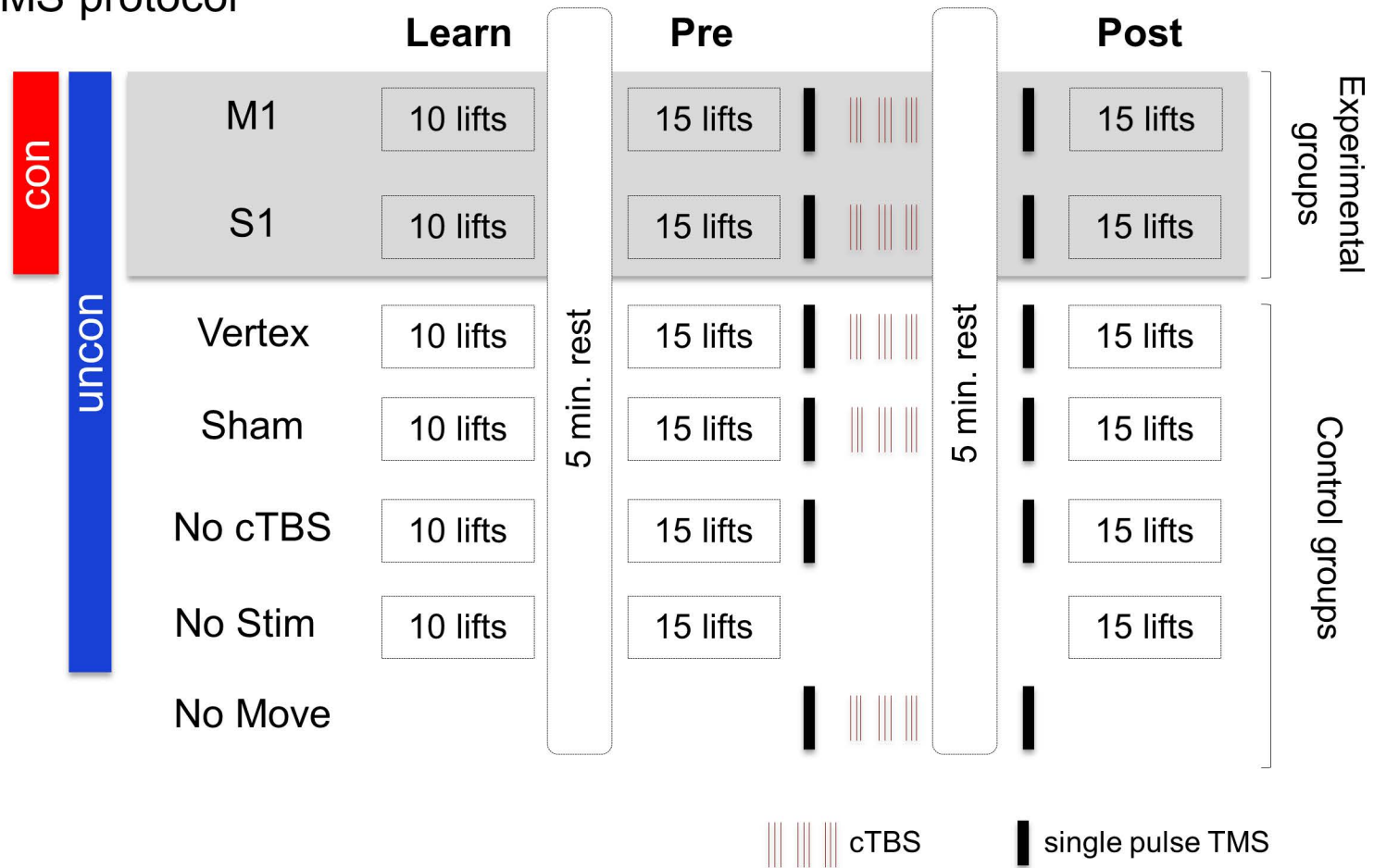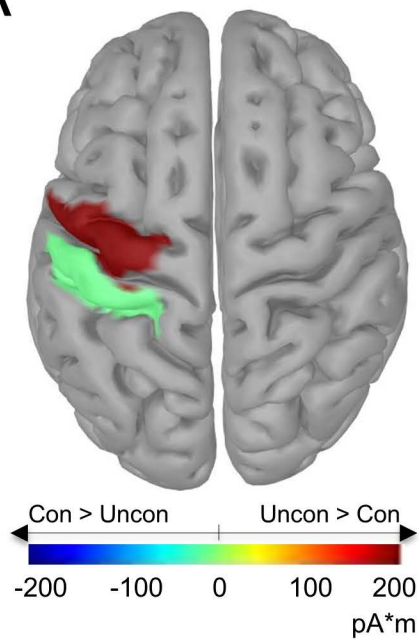
1080

A

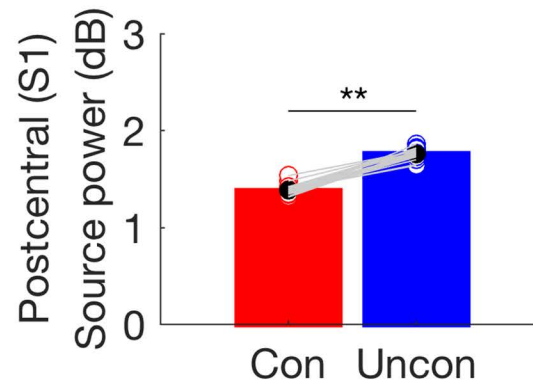**Unconstrained grasp**

61 mm

140 mm

thumb   index f.

Graspable Surfaces

Hidden mass

T_{com}

F_{n2} F_{tan2}

F_{tan1} CoP_2

CoP_1 F_{n1}

CM_0

G

CM_w

l F

T_{ext}

Constrained grasp

20 mm

Hidden mass

T_{com}

F_{tan1} F_{n2} F_{tan2}

CoP_1 CoP_2

F_{n1}

CM_0

G

y

x

CM_w

l F

T_{ext}

B

Reach onset   Contact   Lift-off

Lift switch

CoP (mm)

Thumb
Index f.

Load force (N)

Grip force (N)

T_{com} (N*mm) $\leftarrow T_{ext}$ Roll (°)

Time (s)
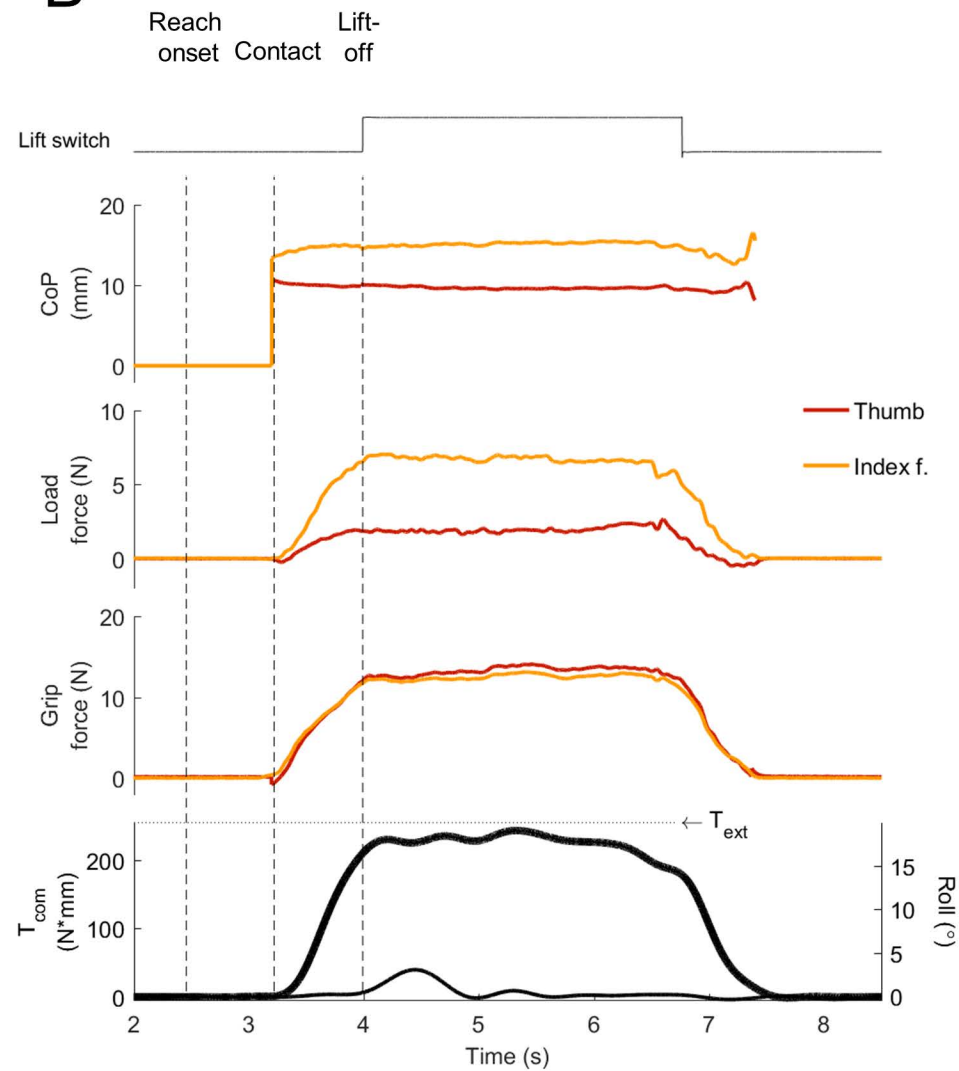
A. EEG protocol

B. TMS protocol

A

B

Precentral (M1) Source power (dB)

Postcentral (S1) Source power (dB)

**

**

Con Uncon

Con Uncon

Con > Uncon   Uncon > Con

-200 -100 0 100 200

pA*m

C

Con

Uncon

M1 ← S1

M1 ← S1

M1 → S1

M1 → S1

GC

0.0   0.03   0.06

A

Learn | Pre block | cTBS | Post block

Compensatory torque (N*mm)

5 min. rest

5 min. rest

← T_{ext}

B

Learn1 Learn5 | Pre1 Pre5 | Post1 Post5

Compensatory torque (N*mm)

**

**   **

— M1 con — M1 uncon — S1 con — S1 uncon — Vertex

A

Compensatory torque (T_{com}) components

| | M1 con | S1 con | M1 uncon | S1 uncon |

d_{LF} (N)

Pre5 / Post1

F_{GF} (N)

d_y (mm)

Time (s)

B

Pre5   Post-cTBS trials

Pre-cTBS: — M1 con — S1 con — M1 uncon — S1 uncon

Post-cTBS: — All groups

In **unconstrained** grasping, **S1** is a critically important component of the grasp network for:
- sensing digit placement
- contributing to assessing whether expected and actual digit placement match each other
- enabling modulation of load force distribution to digit position

In **constrained** grasping, **S1** does not play a major role due to predominant memory-based role for force modulation mediated by M1.

Somatosensory feedback of digit position

S1

Premotor and parietal areas

M1

Memory-based control of digit placement

Is sensed digit placement the same as that used in previous manipulation(s)?

no   yes

Unconstrained grasping

Constrained grasping

Digit force modulation to position

Use sensorimotor memory

Feedback-based modulation of force

Memory-based control of force

load forces

grip force

load forces

In **constrained** grasping, **M1** is essential for:
- storing and retrieving sensorimotor memory of grip and load forces built through previous manipulations

In **unconstrained** grasping, **M1** is essential for:
- retrieval of sensorimotor memory of digit placement built through previous manipulations
- enabling modulation of load force distribution to digit position

.

Supplementary Information

Choice of Contact Points Modulates Sensorimotor Cortical Interactions for Dexterous Manipulation

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Appendix: Supplementary Information

S1. Rationale for design of dexterous manipulation task

Our dexterous manipulation task required subjects to learn to anticipate the effects of a destabilizing external torque (T_{ext}) on the object by exerting a compensatory torque (T_{com}) at object lift onset (1) (Fig. 1*A*). We chose to study task over the classic task of lifting an object with a symmetrical center of mass because the task goal of object roll minimization introduces an element of dexterity in addition to those that have been extensively studied, e.g., modulating normal force to load force to prevent object slip during lift and hold. Importantly, by combining our dexterity requirement with choice of contact points, we had earlier found that digit load force distribution is modulated to variable digit position prior to object lift onset on a trial-to-trial basis (see Introduction). It is important to note that this phenomenon of digit force-to-position modulation is also found when manipulating objects with a symmetrical mass distribution and there is no requirement for exerting a compensatory torque – in fact, in this scenario the covariation between digit load force distribution and position is even stronger than when manipulating objects with an asymmetrical mass distribution (see Fig. 8C (1)). These observations led to the proposition that digit force-to-position modulation is a task- and object-independent phenomenon underlying skilled manipulation through unconstrained grasp contacts (2).

S2. TMS and EEG general procedures

The TMS coil was held tangential to the scalp, perpendicular to the direction of the central sulcus, 45° from the mid-sagittal line, with the handle pointing backward to induce current in the postero-anterior direction (3). Resting motor threshold (rMT) was defined as the TMS intensity that induced 50 μV peak-to-peak motor evoked potentials (MEPs) in 5 of 10 trials in the FDI muscle. Active motor threshold (aMT) was estimated by stimulating M1 at the same site used for rMT while the subject maintained a static contraction using the thumb and index finger on the object at approximately 20% of maximum voluntary contraction, defined as the average of three trials. We defined aMT as the TMS intensity that induced 200 μV peak-to-peak MEPs in 5 of 10 trials in the FDI muscle. For MEP analysis, we removed trials in which EMG activity during the 150-ms window prior to the single-pulse TMS was larger than 2 standard deviations of the mean baseline activity (calculated as the mean of the rectified EMG signal during a short

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period of rest). This was done to ensure that recorded MEP values were not affected by baseline EMG activity at the time of TMS stimulation (4).

Scalp EEG was recorded with a standard 10-20 layout. Sixty channels were recorded from the scalp with an AFz ground and left mastoid reference. Scalp electrodes FT9, FT10, PO9, and PO10 were used to record electrooculogram (EOG) signals, selected based on their distance from our regions of interest. EOG electrodes for horizontal eye movements were placed at the canthus of each eye, while vertical EOG electrodes were placed above and below the left eye. Trial epochs were then created using a time window (−1500 ms to 3000 ms) around the object contact event (time 0). Epochs containing large scalp EMG activity or where subjects did not comply with task instructions were excluded (< 10% of all trials). Electrodes showing abnormally noisy activity were interpolated using a spherical algorithm after applying independent components analysis for artifact rejection.

S3. Digit force modulation to variable position occurs in unconstrained but not constrained grasping.

During the *Learn* and *Pre*-cTBS trial blocks (Fig. 2*B*), subjects from all experimental groups learned to generate compensatory torque (T_{com}) appropriate to minimize object roll. Learning of T_{com} occurred within the first three trials, after which T_{com} was consistently attained (Fig. 4*A*). Trial-to- trial modulation of digit load force distribution (d_{LF}), grip force (F_{GF}) and digit position (d_Y) measured at lift onset was similar to that described in previous work (1, 5, 6). d_Y and d_{LF} from each trial were normalized to generate z-scores and used for linear regression analysis (1) to assess their relation in the EEG (*con* and *uncon* groups; Fig. 2*A*) and TMS experiments (M1 *con*, M1 *uncon*, S1 *uncon*, S1 *con,* and Vertex groups; Fig. 2*B*). Z-scores were computed by normalizing d_{LF} and d_Y for each subject by removing the mean from the value of each trial and dividing the result by the standard deviation.

As T_{com} is learned within the first three trials (1, 5), we used all *con* and *uncon* trials after learning had occurred for the EEG experiment (30 trials for each grasp context per subject), and trials 4-10 of the *Learn* block and all trials in the *Pre* block (22 trials per subject) for the TMS experiment. As expected from our previous work, we found (a) higher d_y variability in all *uncon* than *con* grasping conditions from the EEG and TMS experiments (all $P < 0.05$), and (b) the larger d_Y variability in *uncon* was compensated by trial-to-trial modulation of d_{LF} (25, 27, 30). Specifically, we found significant negative

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correlations between d_{LF} and d_Y only for the *uncon* grasping condition. For the EEG experiment, the *r*-value was –0.51 (*P* < 0.001) for *uncon* and –0.096 (*P* = 0.104) for *con*. For the TMS experiment, we found significant negative correlations between d_{LF} and d_y in M1 *uncon,* S1 *uncon,* and *Vertex* conditions (*r* = –0.45, –0.67, and –0.46; all *P* < 0.0001), but not in M1 *con* and S1 *con* groups (*r* = 0.08 and -0.12, respectively; all *P* > 0.1).

S4. cTBS to M1 and S1 does not reduce corticospinal excitability following exposure to object manipulation.

We found no change in corticospinal excitability (CSE) after continuous theta burst stimulation (cTBS) was delivered over M1 and S1 in the experimental groups (M1 *con*: t_9 = –2.052, M1 *uncon*: t_9 = –2.314, S1 *con*: t_9 = –0.98, and S1 *uncon*: t_9 = –0.991, respectively; all *P* > 0.05), nor M1 in the control groups (*Sham*, *no-cTBS*, and *Vertex*: all *P* > 0.05; Fig. S1).

These findings may seem surprising, as previous work reported a reduction in CSE following cTBS to M1 (7). Unlike our protocol, however, in this previous work subjects did not perform a motor task prior to M1 cTBS. This is an important methodological difference, as a later study by the same group reported no reduction in CSE when subjects performed an isometric force contraction during cTBS stimulation (8). Therefore, the lack of CSE reduction following cTBS in our study, where subjects performed a series of object lifts prior to cTBS, is consistent with the follow-up study by Huang and colleagues (8). Nevertheless, to further validate our cTBS protocol, we performed an additional test on a *No move* group (*n* = 6) where we assessed the effects of cTBS over M1 on MEP size without having subjects perform our manipulation task (Fig. 2*B*). In this group and consistent with previous work where subjects performed no motor tasks prior to M1 cTBS (7), we found a significant decrease in MEP amplitude (t_9 = –7.172, *P* = 0.001; Fig. S1).

S5. cTBS delivered to control groups does not affect compensatory torque.

In addition to the *Vertex* group, we ran three additional control experiments. In each of the control groups described below, participants were given the same task instructions given to subjects in the four experimental groups (Fig. 2*B*).

Sham (*n* = 10): CSE was assessed using single-pulse TMS (spTMS) over contralateral (left) M1 region immediately after the *Pre* block and before the start of the

Post block, corresponding to the time immediately before and 5 minutes after cTBS. cTBS was delivered to a second coil placed immediately behind subject's head with current directed away from the scalp while the coil over contralateral (left) M1 remained in place. Thus, subjects heard the sound elicited by stimulation, but did not experience any somatosensory effect of stimulation on the scalp. This control group was used to control for any somatosensory effects (9) caused by the auditory cue of cTBS on the control of object manipulation.

No cTBS (*n* = 6): This group did not receive cTBS. CSE was assessed using spTMS over contralateral (left) M1 region immediately after the *Pre* block and before the start of the *Post* block. This was done to assess the influence of MEP-induced movements on object manipulation control. Muscle twitches caused by spTMS over M1 have been shown to affect grasping behavior in subsequent lifts (10). Therefore, the results of this control condition were analyzed to ensure that any change in behavior found in the experimental groups was specifically due to a 'virtual lesion' over the cortical area targeted by cTBS.

No Stim (*n* = 6): Neither spTMS nor cTBS were delivered during the experiment.

To assess learning-related changes in T_{com} in control groups, we performed a 4 x 2 between-within repeated measures (rm) ANOVA with *Group* (4 levels: *Sham, no cTBS, No Stim, Vertex*) as the between-subject factor, and *Block* (2 levels: *learn1*, *learn5*) as the within-subject factor. We chose to include the *Vertex* group in this analysis to ensure that there were no differences across any of the control groups. This inclusion also served to validate that having included any control groups in the main analysis with the M1 c*on*, M1 *uncon*, S1 *con* and S1 *uncon* groups would have produced similar results. We report a significant main effect of *Block* ($F_{1,28}$ = 320.46, *P* < 0.05), but no significant *Block × Group* interaction ($F_{1,28}$ = 2.50, *P* > 0.05). Individual rmANOVAs for each group confirmed that the magnitude of T_{com} significantly increased by the end of the *Learn* block (learn1 versus learn5, Fig. S2) for all control groups (significant main effect of *Block,* all *P* < 0.05).

In addition, we confirmed that object manipulation performance remained stable during trials after learning and prior to cTBS using a 4 × 3 between-within rmANOVA with *Group* (4 levels: *Sham, no-cTBS, No Stim, Vertex*) as the between-subject factor, and *Block* (3 levels: *learn5*, *pre1*, *pre5*) as the within-subject factor. After learning, T_{com} remained invariant at the beginning of the *Pre* block (no main effect of *Block*: $F_{2,56}$ = 0.267, *P* > 0.05; no significant *Block × Group* interaction: $F_{2,56}$ = 0.572, *P* > 0.05; Fig.

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S2). This comparison confirmed both that the rest period between the *Learn* and *Pre* blocks had no significant effect on the learned T_{com} (learn5 vs. pre1) and that T_{com} was stable throughout the *Pre* block (pre1 vs. pre5) (Fig. 4*B*). These results are identical to those reported for the experimental groups.

To identify differences across trial blocks and control groups, we used a 4 × 3 between-within rmANOVA with *Group* (4 levels: *Sham, no-cTBS, No Stim, Vertex*) as a between-subject factor and *Block* (3 levels: pre5, post1, post5) as the within-subject factor. We found no main effect of *Block* ($F_{2,56}$ = 2.73, $P > 0.05$) nor significant *Block × Group* interaction ($F_{2,56}$ = 0.42, $P > 0.05$). Lastly, between-group comparisons for all control groups revealed no differences during the *Learn, Pre, or Post* block trials (all $P > 0.05$, Fig. S2). Therefore, subjects in all control groups attained and maintained similar T_{com} throughout the remainder of the *Pre* and *Post* blocks.

Together, these analyses confirms that cTBS to sites other than M1 and S1, and/or the presence of spTMS between blocks, did not affect skilled object manipulation performance. Similar findings were found for peak object roll (see S5).

S6. Persistence of cTBS effects on compensatory torque components is sensitive to grasp context and cortical area.

Analysis of the first post-cTBS trial, as well as subsequenty post-cTBS trials, revealed a differential effect on T_{com} components depending on the cortical area being stimulated and grasp context (Fig. 5*A*,*B*). Therefore, we quantified how these changes in T_{com} components persisted over post-cTBS trials. We used mixed models to examine changes in each T_{com} component over post-cTBS trials using a factor of Group (M1 *con*, M1 *uncon*, S1 *uncon* and S1 *con*) and a continuous covariate of post-cTBS Trial (1-15). For each T_{com} variable, the model used the difference (Δ) of the average of pre5 trials and each post-cTBS trial as the dependent variable.

The results for Δd_{LF} revealed a significant interaction between Group and post-cTBS Trial ($F_{1,3}$ = 3.25, $P < 0.05$). The interaction resulted from a significant difference in slopes between M1 *uncon* and S1 *uncon* groups ($P < 0.05$; Fig. S3, top row). Follow-up examination revealed that both M1 *uncon* and S1 *uncon* exhibited slopes that were different from 0 (both $P < 0.05$). In contrast, the model examining ΔF_{GF} only revealed an effect of Group ($F_{1,3}$ = 8.67, $P < 0.05$). This Group effect is apparent in Fig. S3 (middle row), as the mean level of the line for each group differs at a steady-state across post-cTBS trials. More specifically, follow-up analysis of the intercept revealed only the M1 *con*

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group differed from zero ($P < 0.05$). Therefore, M1 *con* was the only experimental condition with the strongest and more persistent effects of cTBS on F_{GF}. The final model examining Δd_y also yielded a significant interaction ($F_{1,3} = 6.95$, $P < 0.05$; Fig. S3, bottom row). Follow-up analysis revealed that only the slope for M1 *uncon* and S1 *con* groups were significantly different from 0, with both exhibiting a positive trend post-cTBS (both *P* < 0.05).

These findings indicate that the effects of cTBS on digit forces and positions were highly sensitive to the grasp context and cortical area targeted by TMS. Specifically, the persistency of the effects of virtual lesion on T_{com} for M1 *con* grasping throughout all post-cTBS trials (Fig. 5*B*) can be solely attributed to alteration of F_{GF}, as indicated by the persistent and large non-zero intercept across post-cTBS trials (M1 *con*, Fig. S3). In contrast, the faster recovery of T_{com} to pre-cTBS levels for M1 *uncon* grasping can be attributed to the re-establishment of a negative covariation between d_y and d_{LF} (M1 *uncon*, Fig. S3), despite large trial-to-trial fluctuations in d_y (Fig. 5*B*). For the S1 *con* group, the quick recovery of T_{com} to pre-cTBS level after the first post-cTBS trial was mediated only by adjustments in relative positioning of thumb and index finger within the marked contact boundaries on the object (Fig. S3). Lastly, the rate at which T_{com} recovered within the first 10 post-cTBS trials (Fig. 5*B*) following cTBS in the S1 *uncon* group was mostly driven by change in d_{LF} (right column, Fig. S3).
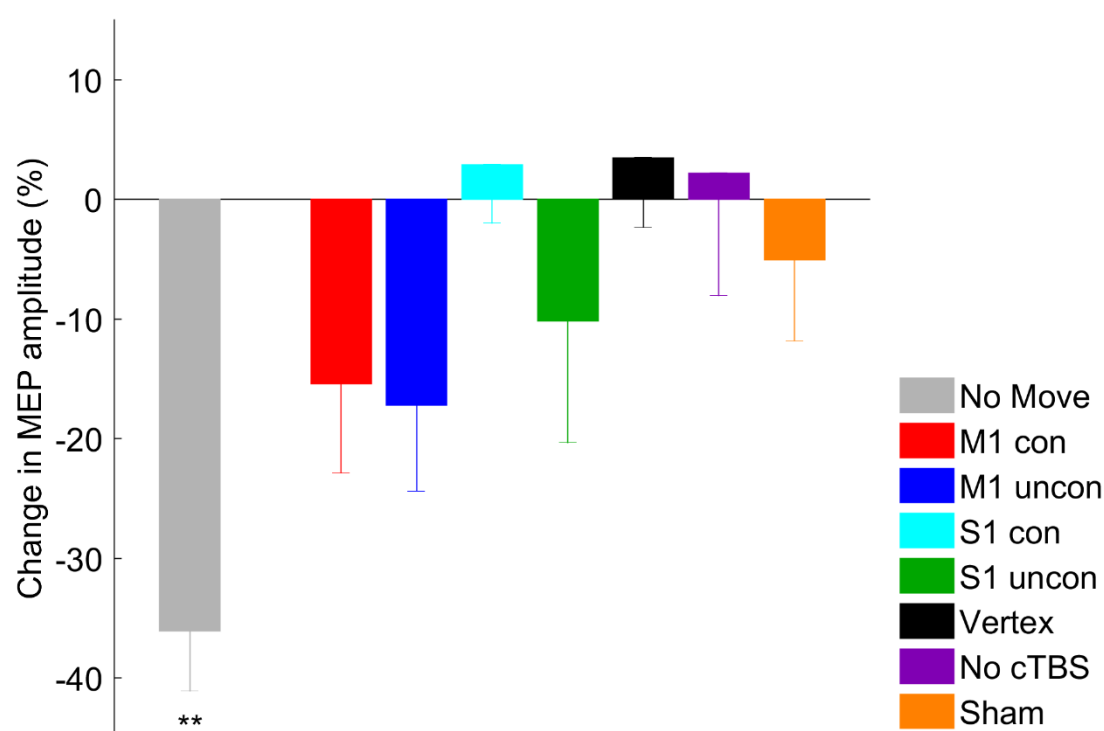
Fig. S1 Corticospinal excitability. Change in CSE was assessed as percentage change in the amplitude of motor evoked potentials (MEP) by comparing pre-versus post-cTBS, or following rest (No Move group). All groups except the No cTBS group received cTBS over M1, S1, or Vertex. ** denotes $P < 0.0125$. Data are averages (± SE) of all subjects.
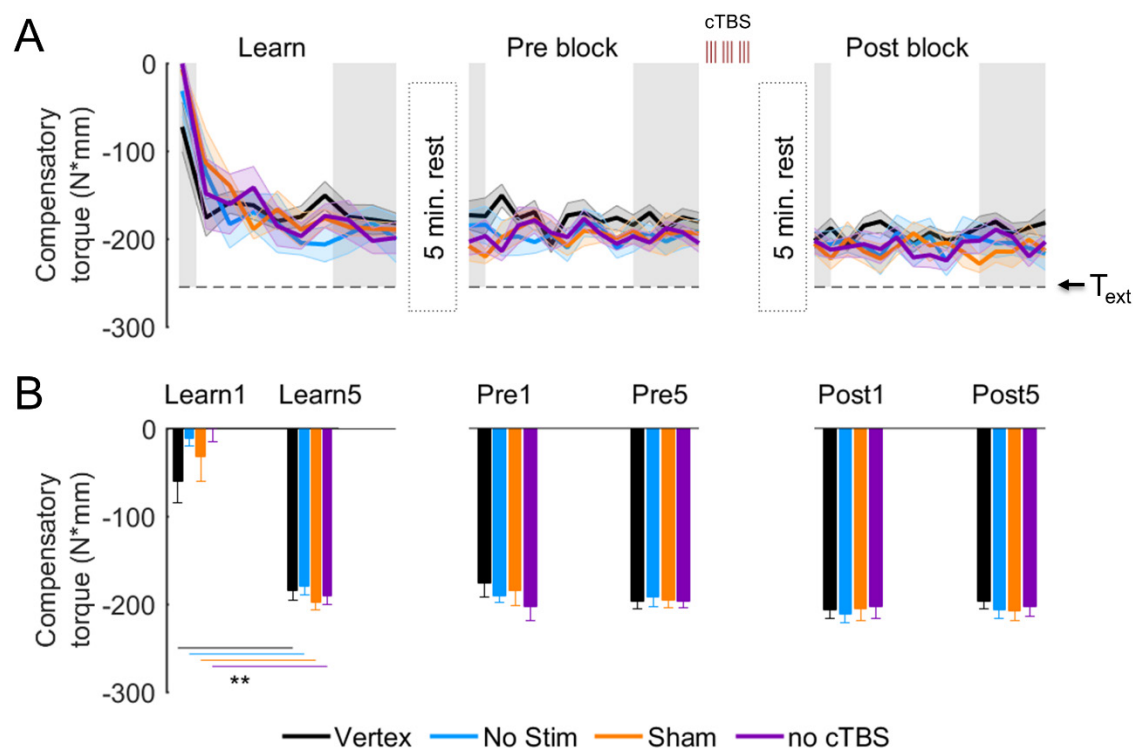
Fig. S2 Compensatory torque: Control groups. (*A*) Compensatory torque (T_{com}) during Learn, Pre, and Post blocks in the Vertex, No Stim, Sham, and No cTBS groups. (*B*) T_{com} on the first trial and the average of the last 5 trials for each block. Data are plotted in the same format as Figure 4. ** denotes $P < 0.0125$.
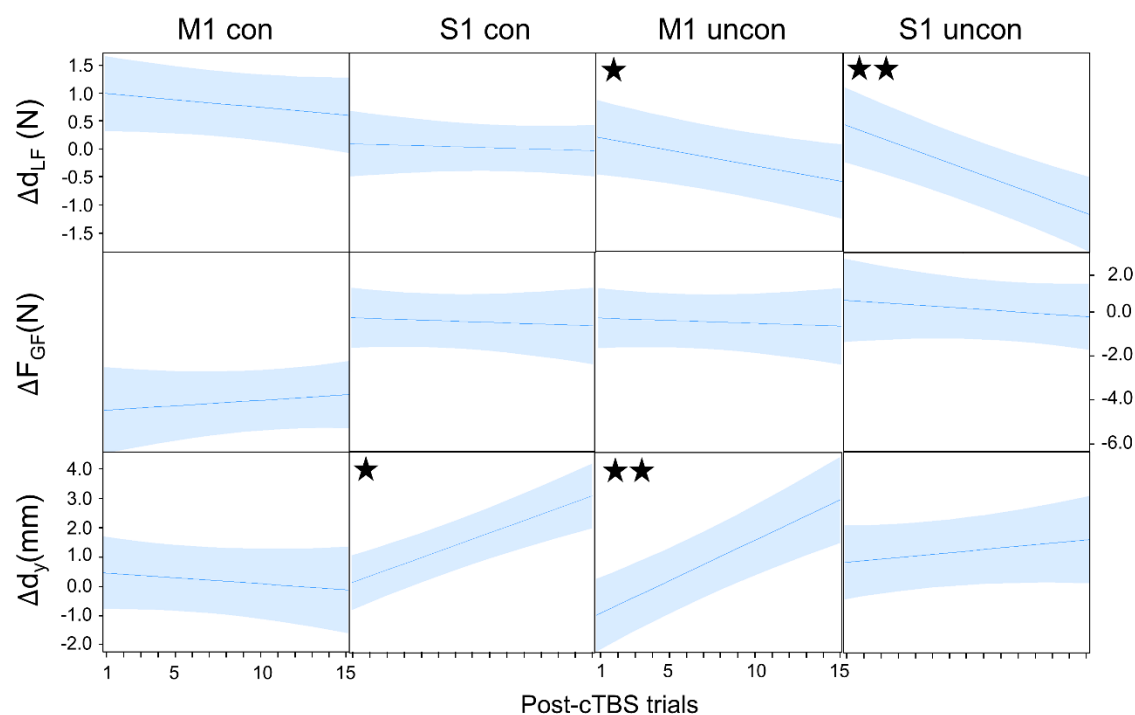
Fig. S3 Effect of cTBS on digit placement, load and grip force. Plots show predicted difference (Δ) between the value of each T_{com} variable averaged across the last five pre-cTBS trials and each post-cTBS trial. Predicted values were obtained by fitting a mixed model that predicted the variable (e.g., d_{LF}) as a function of experimental group and post-cTBS trial. Each plot shows the predicted slope. ★ and ★★ denote a slope significantly different than zero at $P <$ 0.05 and 0.01, respectively.

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