PreSMA stimulation changes task-free functional connectivity in the fronto-basal-ganglia that correlates with response inhibition efficiency

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Running title: Task-free connectivity and efficiency of stopping

1   Previous work using transcranial magnetic stimulation (TMS) demonstrated that the right pre-

2   supplementary motor area (preSMA), a node in the fronto-basal-ganglia network, is critical for

3   response inhibition. However, TMS influences interconnected regions, raising the possibility of

4   a link between the preSMA activity and the functional connectivity within the network. To

5   understand this relationship, we applied single-pulse TMS to the right preSMA during

6   functional magnetic resonance imaging when the subjects were at rest to examine changes in

7   neural activity and functional connectivity within the network in relation to the efficiency of

8   response inhibition evaluated with a stop-signal task. The results showed that preSMA-TMS

9   increased activation in the right inferior-frontal cortex (rIFC) and basal ganglia and modulated

10   their task-free functional connectivity. Both the TMS-induced changes in the basal-ganglia

11   activation and the functional connectivity between rIFC and left striatum, and of the overall

12   network correlated with the efficiency of response inhibition and with the white-matter

13   microstructure along the preSMA – rIFC pathway. These results suggest that the task-free

14   functional and structural connectivity between the rIFCop and basal ganglia are critical to the

15   efficiency of response inhibition.

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22   The ability to stop an on-going action quickly when it is no longer appropriate is an important

23   part of the human executive control function (Logan and Cowan, 1984; Miyake and Friedman,

24   2012). This ability may be significantly impaired with brain disorders and lesions that involve

25   the frontal and basal ganglia system (Aron et al., 2003, Nachev et al., 2007, Sumner et al.,

26   2007, Correa et al., 2010, Dalley et al., 2011, Smith et al., 2011, Sebastian et al., 2012, Benis

27   et al., 2014). Accumulating evidence indicates that such rapid stopping of an on-going action

28   relies on the fronto-basal-ganglia network, including the right inferior frontal cortex (rIFC), and

29   the right pre-supplementary motor areas (preSMA) (Miller and Cohen, 2001, Sumner et al.,

30   2007, Chambers et al., 2009, Aron, 2011).

31

32   Recent work has made significant effort in identifying specific functional roles of the nodes/

33   regions within this inhibitory network. A number of studies have used transcranial magnetic

34   stimulation (TMS), a non-invasive brain stimulation technique (Dayan et al., 2013), to tease

35   apart the causal role of several cortical regions, particularly, the preSMA, and the rIFC during

36   the stopping process (Chambers et al., 2006, Chen et al., 2009, Verbruggen et al., 2010, Cai

37   et al., 2012, Obeso et al., 2013). These studies typically used a variant of the stop-signal task

38   (SST), a well-established experimental paradigm for measuring the ability of stopping an on-

39   going response (i.e., response inhibition) (Logan and Cowan, 1984, Logan et al., 1984). In the

40   SST, participants are instructed to respond as quickly as possible to the primary (or "go")

41   stimuli, but stop/withhold a response when a stop-signal (either an auditory tone or a visual

42   cue) appeared shortly after the onset of the "go" stimulus in a small proportion of the trials. The

43   efficiency of response inhibition is estimated by the stop-signal response time (SSRT)

44   (Verbruggen and Logan, 2008). However, the observed TMS effects on response inhibition are

45 unlikely to be limited to the targeted regions (Obeso et al., 2013, Zandbelt et al., 2013,

46 Watanabe et al., 2015). Studies applying TMS to the right preSMA or rIFC induced changes in

47 cortical excitability of the primary motor cortex (M1) assessed by motor-evoked potentials

48 (Mars et al., 2009, Neubert et al., 2010). Using repetitive TMS (rTMS) over the rIFC or preSMA

49 prior to fMRI scans (i.e., offline rTMS), Zandbelt et al (2013) and Watanabe et al (2015)

50 showed that the stimulation altered activation patterns in the basal ganglia and the

51 supplementary motor complex (SMA), and that significant changes in these regions were

52 predictive of the SSRT during the stop-signal task performance. Although these studies have

53 shown that offline TMS (i.e., stimulation over minutes prior to fMRI) induced changes in

54 network properties over time, to what extent TMS induces immediate changes in patterns of

55 neural activity and task-free functional connectivity within the fronto-basal-ganglia network

56 remains unknown.

57

58 The objective of this study was to examine immediate online changes in neural activity and

59 task-free functional connectivity within the fronto-basal-ganglia network induced by TMS

60 modulation of the right preSMA and the relation of these changes to the efficiency of response

61 inhibition. In addition, we examined whether these changes may, in part, reflect differences in

62 anatomical connectivity that can account for the efficiency of response inhibition (King et al.,

63 2012, Rae et al., 2015). We applied single-pulse TMS during fMRI scans while the subjects

64 were at rest (i.e., online or concurrent TMS-rfMRI). Concurrent TMS-rfMRI offers a window for

65 the observation of changes in neural activity independent of task performance and without

66 compensatory neural adjustments as likely induced in offline rTMS studies (Siebner et al.,

67 2009, Bestmann and Feredoes, 2013). It allows not only the observation of immediate changes

68   in neural activity induced by TMS in remote regions, but also the extent to which TMS affects

69   the network properties including functional connectivity (i.e., temporal coupling of activation)

70   between distant regions (Horwitz, 2003). We applied single pulse TMS at three different

71   intensities (i.e. high=120%, medium=80%, and low=40% of the individual motor threshold) to

72   the right preSMA, a crucial node in the network. The efficiency of response inhibition was

73   assessed using a stop-signal task separately from the concurrent TMS-rfMRI session (see

74   Figure 1 and detailed descriptions of the task and TMS setup in Methods and Materials).

75

76   We expected that changes in the neural activity and the strength of functional connectivity

77   within the network under high-intensity TMS would be correlated with the ability to stop an on-

78   going response (SSRT). We also expected that TMS-induced changes in functional

79   connectivity would likely be correlated with individual differences in anatomical connectivity

80   that can account for response inhibition efficiency.

81

82   **Materials and Methods**

83   Twenty-two healthy subjects (10 males and 12 females) were enrolled in this study. Five

84   subjects were excluded due to significant scan artifacts and data acquisition problems.

85   Seventeen healthy subjects (7 males and 10 females; mean age = 23.7 [±2.7]) were included

86   in the final data analysis. All participants had a normal structural MRI, neurological

87   examination, and were right-handed based on the evaluation with the Edinburgh Handedness

88   Inventory (Oldfield, 1971). All subjects gave their written informed consent to participate in the

89   study, which was approved by the Combined Neuroscience Institutional Review Board at the

90   National Institutes of Health (NIH) and in accordance with the Declaration of Helsinki.

91   Participants received monetary compensation for their time participating in the study.

92

93   Apparatus and procedure. The fMRI scans were performed on a 3.0 T PET/MRI scanner

94   (Biograph mMR software VB17P, Siemens, Erlangen, GER) while the participants were at rest

95   (henceforth, rfMRI). TMS was applied using a Magstim Super Rapid^2 magnetic stimulator

96   (Magstim Company Limited, Whiteland, UK). A Magstim MRI compatible 70 mm TMS coil was

97   mounted on an in-house built MR compatible TMS-coil holder and connected to the Magstim

98   stimulator outside the scanner room through an RF waveguide and with a custom-made ferrite

99   sleeve. The TMS-coil holder included a 10 inch-diameter birdcage fitted with two multi-element

100   matrix MR coils (mMR Body TIM Coils) as the MR signal receiver. Each of the matrix coils

101   included six coil elements with an integrated pre-amplifier. Four rfMRI scans (156 volumes per

102   scan) were acquired using a gradient echo-planar-Imaging (EPI) sequence with a volume TR

103   of 2000 ms followed by a 300 ms pause at the end of each TR (other parameters: TE = 25 ms,

104   flip angle = 90°, phase encoding = P -> A; FOV = 24 cm, acquisition matrix = 64 x 64, slice

105   thickness = 4 mm, and 34 axial slices with interleaved acquisition). Single-pulse TMS was

106   delivered 150 ms after the onset of the 300 ms pause period (see Figure 1a). To monitor any

107   potential shift of TMS-coil position throughout the scan session, three radiographic markers

108   were placed on each subject's head in addition to head restraints (subject's head was strapped

109   to the TMS-coil holder to insure a direct contact with the TMS coil and minimize head

110   movement). A short (< 15 sec) marker-alignment scan (TR = 330 ms, TE = 1.33 ms, flip angle

111   = 15°, FOV = 22 cm, slice thickness = 2 mm, slices = 80 per slab, acquisition matrix = 256 x

112   256) was acquired immediately before and after the four EPI scans. These marker scans were

113   used to provide an additional estimate of the shift in the head position relative to the TMS-coil

114   at the end of the scan session (see Figure 1 in Supplementary material for examples of marker

115   locations and images of the marker-alignment scans from a representative participant. Also

116   see Table for MR signal quality indexes). On average, the subjects' head movement was

117   minimum (translation: x < 0.1 mm [± 0.2], y < 0.3 mm [± 0.5], z < 0.2 mm [± 0.6]; and rotation: <

118   0.01 mm [± 0.01] in x, y, z directions). A gradient echo EPI fieldmap and a high resolution

119   (1×1×1 mm) T1-weighted anatomical image were also acquired (TR = 2900 ms, TE = 3.03 ms,

120   TI = 1100 ms, FOV = 256 mm, flip angle = 7⁰, acquisition matrix = 256 x 256, slices = 176 per

121   3D slab, slice thickness = 1 mm) for unwarping and normalizing the EPI images to a template

122   brain. In addition, diffusion tensor imaging (DTI) data were acquired for each participant with

123   the following scan parameters: TR = 1700 m, TE = 98 ms, FOV = 256 mm, acquisition matrix =

124   128 x128, slice thickness = 2 mm, 90 slices without gap, acceleration factor = 2, 10 volumes of

125   b value = 0 s/mm^2, 10 diffusion directions with b value = 300 s/mm^2, and 60 diffusion directions

126   with b value = 1100 s/mm^2. In addition, a T2-weighted scan with Fast Spin Echo sequence and

127   fat suppression (TR = 5000 ms, TE = 83 ms, FOV = 220 mm, acquisition matrix = 256 x 204,

128   flip angle = 120⁰, slices = 90, slice thickness = 2 mm) was acquired for each subject at 1.7 mm

129   isotropic voxels to be used as a structural target in post-processing.

130

131   The TMS stimulation site (i.e. right preSMA) was determined for each participant based on the

132   participant's own T1 anatomical MR images using a stereotactic navigation system (Brainsight

133   by Rogue research, Inc., Montreal, Canada). It has been shown that preSMA stimulation

134   induces little discomfort and minimal facial muscle movement relative to other regions (e.g.,

135   IFC) (Sandrini et al., 2011). The center of the TMS coil was placed over the right preSMA, 1

136   cm anterior to the vertical line from the anterior commissure (AC) perpendicular to the anterior

137   – posterior commissure line in the sagittal plane (see Figure 1a and also Tremblay and

138   Gracco, 2009). The localization of the center of the TMS coil to the target (the right pre-SMA in

139   native space: x = 10, y = 10) was carried out using the subjects' own MR T1 structural image

140   and the stereotaxic neuronavigation system "Brainsight." The distance between the TMS target

141   location on the scalp and the vertex (Cz) was also calculated for each subject (mean distance

142   = 4.5 cm [± 0.14]) and used to mark the TMS target site on a swim cap worn by participants

143   during the concurrent TMS-rfMRI session. This distance (> 4 cm) is consistent with previous

144   studies showing the approximate distance between the vertex and the pre-SMA (Picard and

145   Strick, 1996, Mars et al., 2009, Arai et al., 2011). The TMS coil was oriented in line with the

146   longitudinal fissure and with the coil handle pointed posteriorly. Prior to the experiment, the

147   resting motor threshold (rMT) of each participant was determined using the same MRI

148   compatible TMS coil. The individual rMT was set as the lowest intensity of TMS stimulation

149   applied over the left primary motor cortex that was capable of evoking a visible contraction in

150   the relaxed right first dorsal interosseous muscle on at least 5 out of 10 consecutive

151   stimulations (Pridmore et al., 1998). The average rMT was 66.5% of the maximum stimulator

152   output. In order to examine TMS specific effects on the BOLD signal change, three different

153   stimulation intensities were used during the TMS- rfMRI scans: 40%, 80%, and 120% of each

154   participant's own rMT. Thirty single-pulse TMS (10 for each intensity) were delivered semi-

155   randomly with a jittered inter-stimulus-interval (ISI range: 9.2 – 13.8 seconds) during each

156   rfMRI scan. Four scan runs (< 6 min each) were acquired for each subject with a total of 120

157   TMS pulses (10 x 4 pulses per TMS intensity).

158

159   Behavioral task and data analysis. Subjects performed in a separate experimental session, at

160   least 24 hours prior to the TMS-rfMRI session, a variant of the stop-signal task (SST) used in a

161   previous study (Xu et al., 2015). They were instructed to stop their response when a visual cue

162   (i.e., a stop-signal) appeared after the response ("go") stimulus onset. The stimulus was either

163   a left or right pointing arrow with a "+" sign in the middle (see Figure 1b). Participants were

164   instructed to make a response (i.e., a "go" response) as quickly as they could according to the

165   arrow direction by pressing either the left or the right key on a response box. For 25% of the

166   trials, the "+" sign (i.e., the stop-signal) turned red after the stimulus onset with a short delay

167   (i.e., the stop-signal delay or SSD). The SSD was dynamically controlled based on whether a

168   successful (stop-inhibit) or an unsuccessful (stop-respond) response was made (Verbruggen

169   and Logan, 2008). The SSD was set at 100 msec (the shortest SSD) for the first Stop trial and,

170   then a staircase tracking method was implemented such that for every successfully-stopped

171   (i.e., Stop-inhibit) response, the SSD was increased by 50 msec to make it harder to stop on

172   the next trial, and for each fail-to-stop (i.e., Stop-respond) trial, the SSD decreased by 50

173   msec. The longest possible SSD was 450 msec. The stop-signal response time (SSRT), a

174   measure of the efficiency of response inhibition, was estimated for each participant by

175   subtracting the mean SSD from the nth (where n is the percentile corresponding to the

176   probability of the Stop-respond trials) fastest RT of the primary "go" responses (Logan, 1994).

177   The SSRT was then correlated with the TMS-induced rfMRI BOLD activation, the strength of

178   functional connectivity of the fronto-basal-ganglia network, and with the DTI white-matter

179   microstructure indexes (i.e., the fractional anisotropy [FA], fiber track counts, and averaged

180   fiber length). Recent studies have shown that these microstructure indexes including fiber

181   bundles and fiber length may be associated with cognitive functions (Marner et al., 2003,

182   Behrman-Lay et al., 2014). One participant had unusually short SSRT (88 ms) although all

183   other scores were in the normal range. Therefore, the SSRT of this participant was excluded in

184   all correlation/regression analyses to avoid statistical bias.

185

186   MRI data processing and analysis. The rfMRI data were processed and analyzed using the

187   SPM8 software (the Wellcome Department of Imaging Neuroscience, University College

188   London, UK). All images were EPI distortion corrected with a gradient echo EPI fieldmap

189   collected during the concurrent TMS-rfMRI session, and slice-timing corrected, realigned, and

190   coregistered with the subject's own high resolution T1 anatomical image. All subjects' T1

191   images were combined to generate a T1 template using the DARTEL software and

192   procedures, and normalized to the MNI (Montreal Neurological Institute, Canada) template.

193   The normalization parameters from each subject were then applied to the normalization of the

194   subject's own EPI images. The normalized EPI images were smoothed using an 8x8x8 mm

195   FWHM kernel. At the first level analysis, the design matrix included four scan runs/sessions

196   and three TMS intensity conditions (Low [40%], Mid [80%], and High [120%]) plus six motion

197   parameters as confounds. The fMRI activation was modeled using the canonical hemodynamic

198   response function (HRF) with temporal and dispersion derivatives. The data were high-pass

199   filtered at 128 Hz and the epoch/event duration was set at 1 sec. Contrasts (i.e., t-tests: Low –

200   baseline, Mid – baseline, and High – baseline) from the first level individual analysis were fed

201   into the second (group) level analysis using one-way within-subject ANOVAs. Analyses with

202   the whole brain and a priori regions of interest (ROIs) with a binary mask that included the

203   fronto-basal-ganglia inhibitory network (i.e., the SMA, preSMA, right IFC, and the basal

204   ganglia) were performed (the ROI mask was created in the MNI template space using the

205 WFU PickAtlas software by the Functional MRI Laboratory at the Wake Forest University

206 School of Medicine, NC). Additional contracts (t tests) were performed to examine the extent of

207 changes in distal activation induced by the three TMS intensities with focus on brain regions

208 showing a monotonic increase or decrease in BOLD signal. All statistical contrasts were

209 corrected for multiple comparisons using the topological false-discovery rate (FDR) (Chumbley

210 and Friston, 2009, Chumbley et al., 2010) and all reported significant voxels survived a

211 corrected threshold of $p < 0.01$. Voxels showing a significant monotonic change in the preSMA,

212 SMA proper, rIFC, and the basal ganglia of the network were extracted (8 mm diameter sphere

213 centered on the peak of each cluster) to further examine the relationship between the TMS-

214 induced BOLD signal change and the efficiency of response inhibition (i.e., the SSRT).

215

216 To examine the effect of TMS intensity on functional connectivity within the inhibitory network

217 and the extent to which the connectivity strength may be associated with the efficiency of

218 response inhibition, we performed regional functional connectivity analyses. Partial Least

219 Square Regression (PLSR) analysis (McIntosh and Lobaugh, 2004, Krishnan et al., 2011) was

220 performed to estimate the coupling of the BOLD signals between seven regions in the

221 inhibitory network: the right preSMA, rIFC opercularis (rIFCop), right striatum (rStri), left

222 striatum (lStri), left pallidum (lPal), right pallidum (rPal), and bilateral subthalamic nuclei (STN)

223 (Figure 4a). The right preSMA was defined as a sphere (8mm in diameter) centered in the

224 TMS targeted region (MNI xyz = 10, 10, 50). The remaining regions were defined using binary

225 masks created in the MNI template space using the WFU PickAtlas software. The connectivity

226 analysis between two additional regions outside the network (i.e., the right dorsal lateral

227 prefrontal cortex [rDLPFC], and the right inferior-parietal cortex [rIPC]) was also included as a

228 control. The control region, rDLPFC (8mm sphere, MNI coordinate: xyz = 37, 33, 32), was

229 determined based on previous studies showing its functional connection with the rIPC in

230 executive control processes (Cieslik et al., 2013). It is adjacent to the fronto-basal-ganglia

231 network and anatomically connected with the right preSMA (Nachev et al., 2008), but its

232 connection with the rIPC is not response inhibition specific. We expected that TMS-induced

233 changes in the connectivity between the rDLPFC and rIPC, if any, would not be predictive of

234 the efficiency of response inhibition. For each subject, trial-based regression coefficients (i.e.

235 beta series) (Rissman et al., 2004) from each voxel were extracted from the first level analysis

236 for each TMS intensity level. PLSR was then used to estimate the connectivity between the

237 right preSMA and the other regions as well as between rIFCop and the ROIs in the basal-

238 ganglia (i.e., rStri, lStri, rPal, lPal, and STN), and the connectivity of the control connection

239 between the rDLPFC and rIPC. The regression coefficient between the first extracted PLS

240 temporal components for each analysis was used as an index of inter-regional connectivity.

241 The low intensity TMS condition served as a baseline control for nonspecific effects of TMS as

242 done in previous concurrent TMS-fMRI studies (Feredoes et al., 2011, Heinen et al., 2014).

243 The analysis of the effect of TMS intensity on changes in connectivity focused on the maximal

244 difference between the High and Low TMS conditions using planned t-tests with the standard

245 Fisher's z transformed correlation coefficients of the connectivity index. Linear regression

246 analyses were also performed between the averaged connectivity index for the two TMS

247 intensity conditions and the efficiency of response inhibition (SSRT) to examine the extent to

248 which the task-free connectivity within the network was predictive of the SSRT.

249

250   The DTI data were preprocessed with the TORTOISE software (by the Pediatric Neuroimaging

251   Diffusion Tensor MRI Center at the National Institutes of Health, www.tortoisedti.org) for

252   volume realignment, eddy current correction, EPI distortion correction, and non-linear tensor

253   fitting (Basser et al., 1994, Pierpaoli et al., 2010). The preprocessed FA maps were normalized

254   to the MNI (Montreal Neurological Institute, CA) template space using the TBSS (Tract-Based

255   Spatial Statistics) nonlinear registration procedure of the FSL software (by the FMRIB Analysis

256   Group, University of Oxford, UK). Deterministic tractography was performed using the Diffusion

257   Toolkit (DTK) software (by the TrackVis.org, Martinos Center for Biomedical Imaging,

258   Massachusetts General Hospital) with normalized tensor images in the MNI space. The fiber

259   tacks were determined using the FACT method (fiber assignment by continuous tracking) with

260   the termination angle set at 35 degrees to minimize false positives. Both the FA and DTK track

261   maps were then used to examine the white-matter microstructure and its relation to the

262   efficiency of response inhibition and the TMS-induced change in functional connectivity. For

263   the objectives of the study, we focused on the white-matter regions near the right preSMA (the

264   locus of TMS) and rIFCop that are known to have direct fiber connections between the

265   preSMA, rIFCop, and basal ganglia (Aron et al., 2007, Catani and Thiebaut de Schotten, 2008,

266   Catani et al., 2012, King et al., 2012). Two seed ROI masks (8mm radius) were created

267   between the right preSMA and rIFCop (see Figure 5) that have been shown to have major fiber

268   bundle connections (see Catani et al., 2012; Leunissen et al., 2013). The two seed ROIs (in

269   MNI space: ROI 1 [near right preSMA] = 12, 16, 50; ROI 2 [near rIFCop] = 30, 8, 22) were

270   placed in the individual DTK track maps. The estimations of fiber counts and fiber length were

271   determined by constraining/including only fibers that originated in both seed ROIs. In addition,

272   two mirror seed ROIs and analyses were applied to the left hemisphere to examine whether

273   there was any hemispheric specificity in relation to the TMS-induced change of functional

274   connectivity.

275

276   **Results**

277   Behavioral performance of the stop-signal task. On average, the participants made 49% ($\pm$

278   4.7%) of the stop-inhibit (i.e., successfully stopped) responses, the mean SSRT = 195 ($\pm$ 37)

279   ms (within the normal range, see Logan, 1994), the mean SSD = 218 ms ($\pm$ 57), the observed

280   average Stop-respond (i.e., fail-to-stop response) RT = 378 ($\pm$ 81) ms, the estimated Stop-

281   respond RT = 412 ($\pm$ 34) ms, and the averaged "go" RT = 415 ms ($\pm$ 35). Consistent with

282   previous studies using the stop-signal task, the correlation between the SSRT and the "go" RT

283   was not significant (R^2 = 0.18, p <0.1).

284

285   TMS-rfMRI results. Figure 2 shows the results of the analysis using a priori ROIs within the

286   fronto-basal-ganglia network (also see the whole brain results in Figure 2 of the

287   Supplementary Material). The results showed that multiple regions within the network had a

288   significant (FDR < .01) monotonic increase of BOLD signal change as the TMS intensity

289   increased. These regions included the right preSMA, SMA proper, rIFC (opercularis), right

290   caudate, putamen, pallidum, and the left caudate. Except for the right preSMA and the SMA

291   proper which were directly under or very close to the TMS coil, all regions showed a significant

292   monotonic increase in the BOLD signal. Two one-way within-subject ANOVAs performed

293   separately for these regions showed a significant main effect of TMS intensity (increase in

294   signal: $F_{(2,32)}$ = 22.1, MSe = 7.8, p < .0001; decrease in signal: $F_{(2,32)}$ = 21.2, MSe = 9.5, p <

295   .0001). Post hoc Scheffe's F test (p < .05) showed that the BOLD signal change (%) under the

296   three TMS-intensity conditions differed significantly from each other (positive trend: Low TMS =

297   -1.32%, Mid TMS = 0.16%, High TMS = 1.55%; negative trend: Low TMS = 1.42%, Mid TMS =

298   -0.56%, High TMS = -3.43%). Separate one-way within-subject ANOVAs for each of these a

299   priori ROIs (with TMS intensity as the within-subject factor) showed a significant main effect of

300   TMS intensity for all these regions. Post hoc F test ($p < .05$) showed significant differences

301   between the TMS conditions for each of these regions within the network (see Figure 2 for

302   details). Figure 3 further shows that in the High and the Mid TMS conditions, the BOLD signal

303   change in the basal-ganglia regions (the left caudate and the right pallidum) had significant

304   correlations with the SSRT (the right pallidum: High TMS $t_{14} = -3.18$, $R^2 = 0.42$, $p < 0.01$; Mid

305   TMS $t_{14} = -2.8$, $R^2 = 0.36$, $P < 0.05$; and the left caudate: High TMS $t_{14} = -2.43$, $R^2 = 0.30$, $p <$

306   0.05). When all the basal-ganglia regions were combined, the BOLD signal change again

307   showed significant correlation with the SSRT (High TMS: $t_{14} = -2.56$, $R^2 = 0.32$, $p < 0.03$; Mid

308   TMS: $t_{14} = -2.18$, $R^2 = 0.25$, $p < 0.05$), indicating that, at least in the High and Mid intensity

309   conditions, TMS may induce significant change in neuronal activity distal to the stimulation site

310   within the inhibitory network that are predictive of response-inhibition efficiency.

311

312   In addition to the TMS intensity effect on the BOLD signal change and its correlation with the

313   SSRT, Figure 4b shows that the overall connectivity of the High TMS condition (0.76) was

314   significantly higher than the Low (0.70) TMS condition (paired t-test: $t_{16} = 1.95$, $p < .05$).

315   Planned t-tests for each of the connections between the High and Low TMS intensities showed

316   a significant difference in the connectivity of preSMA - rIFCop ($t_{16} = 2.23$, $p < .03$), rIFCop -

317   lStri ($t_{16} = 1.8$, $p < .05$), rIFCop – rPal ($t_{16} = 1.95$, $p < .04$), rIFCop – lPal ($t_{16} = 1.87$, $p < .04$),

318   and of rIFCop – STN ($t_{16} = 1.81$, $p < .05$). The connectivity for these connections was

319   significantly stronger in the High TMS condition (.90, .84, .77, .79, and .79) than the Low

320   condition (.79, .77, .70, .71, and .68). Separate linear regression analyses using the overall

321   (averaged) connectivity of all connections as the predictor variable showed a significant

322   negative correlation with the SSRT (t_{14} = -2.12, R^2 = .24, p < .05) in the High but not the Low

323   TMS condition (R^2 = .03). These results indicated a significant relationship between the task-

324   free network connectivity and the efficiency of rapid response inhibition.

325

326   We further examined the relationship between the SSRT and the connectivity of each of the

327   connections that showed significant TMS effect (Figure 4a, thicker lines). The results of a

328   multiple regression analysis that included all these five connections showed that only the

329   connectivity of rIFCop - lStri accounted for a significant amount of the variance in the SSRT (t_{10}

330   = -2.50, R^2 = .38, p < .03) (see Table 1). Simple regression analysis again showed a significant

331   negative correlation between the SSRT and the rIFCop – lStri connectivity (t_{14} = -2.25, R^2 =

332   .27, p < .05). As the connectivity increased, the SSRT decreased (see Figure 4). None of these

333   connectivity measures was significantly correlated with the "go" RT which is not response

334   inhibition specific. There was also no significant correlation between the SSRT and the control

335   connection rDLPFC - rIPC, a link outside the fronto-basal-ganglia network. The High and Low

336   TMS intensity did not have significant effect on the strength of this connection either even

337   though the rIPC was sensitive to the TMS intensity (see Figure 2 in the Supplementary

338   Material for results from the whole-brain analysis).

339   ---

340   Insert Table 1 about here

341   ---

342   Based on the results of the TMS-intensity effect on the functional connectivity and its relation

343   to the response-inhibition efficiency (SSRT), we further examined individual differences in the

344   white-matter microstructure (reflected in the fiber counts, fiber length, and FA) and its relation

345   to functional connectivity and response-inhibition efficiency. Pearson correlations were

346   performed between the fiber counts or length and all the connections (i.e., preSMA - rIFCop,

347   rIFCop - lStri, rIFCop – rPal, rIFCop – lPal, rIFCop – STN, and the overall network

348   connectivity) that showed significant change in functional connectivity under the High TMS

349   condition. The results (Figure 5a) showed significant positive correlations between the fiber

350   length and functional connectivity of the overall network connectivity ($p < .01$, $R^2 = 0.35$),

351   rIFCop – lStri ($p < .05$, $R^2 = 0.24$), and rIFCop – rPal ($p = .05$, $R^2 = 0.23$). As the fiber length

352   increased, functional connectivity increased. There was also a significant negative correlation

353   between the fiber length and the SSRT ($t_{14} = -2.53$, $R^2 = .31$, $p < .03$), that is, the longer fiber

354   length was associated with more efficient response-inhibition process (or shorter SSRT). There

355   was no significant correlation between fiber length and the "go" RT ($p < .2$), nor were there

356   significant correlations between the fiber counts and functional connectivity or the behavioral

357   measures. The fiber counts and length indexes from the left hemisphere also did not correlate

358   with the TMS-induced functional connectivity or the SSRT. Here, we would like to add a caveat

359   of caution in regard to the results of the relationship between the functional and structural

360   connectivity. Although the less stringent statistical correlational analyses revealed significant

361   relationships between the functional and structural connectivity, this study included a relatively

362   small sample of subjects. Therefore, the statistical approach is rather exploratory and,

363   consequently, the results should also be viewed as such. Future studies with larger samples

364   may provide more conclusive analysis.

365

366 In addition to the fiber track analysis, we extracted averaged FA values from the same seed

367 ROIs in the right hemisphere using the coregistered and normalized FA maps (Figure 5b). The

368 results of the linear regression analyses showed significant correlations between the mean FA

369 values of both these ROIs and the SSRT (ROI 1: t_{14} = -2.2, p < .05, R^2 = .26; ROI 2: t_{14} = -2.52,

370 p < .03, R^2 = .31). The FA and the SSRT results indicated a significant relationship between

371 the white-matter microstructure and the efficiency of response inhibition. Again, no significant

372 correlations were observed between the FA values and the "go" RT.

373

374 **Discussion**

375 In the current study, we applied single-pulse TMS at three different intensities to the right

376 preSMA during fMRI scans while the subjects were at rest. This task-free concurrent TMS-

377 rfMRI revealed, for the first time, immediate effects of TMS on neural activity and task-free

378 functional connectivity within the fronto-basal-ganglia network, and their relation to the

379 efficiency of response inhibition (SSRT) that are not confounded by compensatory neural

380 adjustments or task-related neural activity.

381

382 The results of the study showed TMS-induced BOLD signal increase in multiple brain regions

383 within the inhibitory network including the rIFC, caudate, putamen, and the right pallidum. The

384 BOLD signal change induced by high-intensity TMS in the right pallidum and left caudate also

385 correlated with the SSRT, but not with the task response (or "go" response) in general. These

386 results suggest that the widespread effect of preSMA TMS, at least at the suprathreshold level,

387 on the patterns of neural activity beyond the targeted region (i.e., the right preSMA) was

388 immediate and related to the task-free neural activity associated with response inhibition.

389 Although we cannot rule out completely that the observed effect was not due to subjects'

390 anticipation of the onset of the various TMS pulses, all things being equal, such anticipatory

391 activity would be constant for all three types of stimuli most of the time, at least, with the

392 jittered stimulus presentation timing.

393

394 More importantly, our results also showed that relative to the Low TMS condition, High

395 preSMA-TMS induced immediate changes in the coupling of the rfMRI activation (i.e.,

396 functional connectivity) between preSMA and rIFCop, and between the rIFCop and the basal

397 ganglia (i.e., striatum, pallidum, and STN). In the High TMS condition, the SSRT also

398 significantly correlated with the connectivity between the rIFCop and left striatum, and with the

399 mean connectivity of all the connections combined, indicating the impact of preSMA TMS on

400 the task-free functional connectivity of the network as a whole and the response inhibition

401 process (also see Kahan et al., 2014 for STN stimulation). The preSMA-TMS effect on

402 functional connectivity appeared to be more specific to response inhibition relative to the "go"

403 response that did not require inhibition. No significant correlations were observed between the

404 functional connectivity and "go" RT. The functional connectivity between the rDLPFC - rIPC, a

405 control link outside the fronto-basal-ganglia network, also did not correlate with the SSRT,

406 even though the rIPC activation was sensitive to the TMS intensity.

407

408 These results indicate a functional link between the preSMA and remote activation within the

409 network, and between the preSMA and the task-free functional connectivity of the network. In

410 addition, the preSMA TMS appeared to affect directly its functional connectivity with the rIFCop

411   more than with other regions within the network. However, the change in the task-free

412   functional connectivity between the preSMA and rIFCop coincided with significant changes in

413   the functional connectivity between the rIFCop and the basal ganglia (i.e., lStri, lPall, rPall, and

414   STN). Although the effect of the preSMA TMS on response inhibition is likely the result of

415   complex interactions among varying levels of altered neuronal activity in multiple

416   regions/nodes within the network, we postulate that functional connectivity between the

417   preSMA and rIFCop itself significantly influences the functional connectivity within the network,

418   particularly, between the rIFCop and the basal ganglia. It is possible that in the context of

419   making a rapid stopping response, preSMA communicates directly with the rIFCop as well as

420   STN, which in turn, induces coordinated neural activity between the rIFCop and the basal

421   ganglia to achieve the rapid stopping response. Consequently, the functional connectivity

422   between the rIFCop and striatum, and the BOLD signal change in the basal ganglia were

423   predictive of the SSRT. This is consistent with previous work showing an interdependent

424   relationship between the preSMA and rIFCop, and the importance of the rIFCop during the

425   inhibition process (Duann et al., 2009, Neubert et al., 2010, Zandbelt and Vink, 2010, Zandbelt

426   et al., 2013, Aron et al., 2014, Picazio et al., 2014).

427

428   The observed changes in the task-free functional connectivity and their relation to the stopping

429   response suggest a possible mechanism underlying the efficiency of response inhibition. We

430   speculate that the strength of the task-free functional connectivity between the nodes within

431   the network may be critical for regulating the efficiency of the stopping process. Differential

432   effects of TMS loci (e.g., right preSMA vs rIFC) on the task-free functional connectivity may

433   explain why previous studies applying TMS to the preSMA and the rIFC resulted in

434   inconsistent observations regarding the role of these nodes in the stopping process

435   (Rushworth et al., 2002, Chambers et al., 2006, Chambers et al., 2007, Chen et al., 2009,

436   Verbruggen et al., 2010, Cai et al., 2012, Obeso et al., 2013, Zandbelt et al., 2013). Recent

437   studies showed that suprathreshold TMS could significantly increase the power of the natural

438   frequency of the electrophysiological oscillations associated with neural activity both local and

439   remote to the stimulation site (Rosanova et al., 2009, Pellicciari et al., 2013, Kundu et al.,

440   2014, Pripfl et al., 2014). Rosanova et al (2009) reported that single-pulse TMS over three

441   separate cortical sites (Brodmann areas 19, 7, and 6) of the corticothalamic network induced

442   local and long-range neural activity with beta, alpha, and gamma oscillations of the natural

443   frequency range differentially associated with these regions. Picazio et al (2014) also reported

444   that inhibiting a "no-go" response was associated with frequency oscillations at the beta range

445   from the rIFC relative to the "go" response. Some evidence from intracranial

446   electroencephalography studies indicated that specific neuronal oscillation frequencies (e.g.,

447   the beta and gamma band) were directly associated with stopping responses (Swann et al.,

448   2009, Swann et al., 2012). Swann et al (2012) reported that intracranial electric stimulation of

449   the preSMA in a patient evoked strong local field potentials and an increase in the beta band

450   frequency in the rIFC that was associated with the successful stopping responses. STN

451   stimulation at rest has also been shown to induce beta oscillatory activity in the rIFC and

452   modify effective connectivity (i.e., with causal influence) between multiple regions within the

453   fronto-basal-ganglia network (Swann et al., 2011, Kahan et al., 2014). There is substantial

454   evidence indicating a direct association and cognitive/functional relevance between the BOLD

455   signal change and neuronal synchronization across a wide range of frequencies and frequency

456   power (Scheeringa et al., 2011, Sadaghiani et al., 2012). Functional connectivity is likely

457   critical to cognitive processes including rapid response inhibition. If the preSMA TMS not only

458   changes patterns of neural activity but also modifies the frequency power associated with the

459   task-free functional connectivity of remote regions, it is likely that the TMS-induced activity in

460   regions within the fronto-basal-ganglia network would affect the efficiency of response

461   inhibition when the preSMA TMS is applied during experimental tasks. However, it would be

462   important in future studies to determine how stimulation of other nodes in the network (e.g.,

463   rIFC) may influence network dynamics.

464

465   Related to the influence of task-free functional connectivity on response inhibition, recent

466   studies have also demonstrated some degree of correspondence between the functional and

467   anatomical connectivity of the human brain (Baird et al., 2005, Rykhlevskaia et al., 2008,

468   Honey et al., 2010, Johansen-Berg, 2010). The preSMA-TMS effect on network activity and

469   response inhibition may also be influenced by the individual differences in the anatomical

470   connectivity. It is known that preSMA has direct white-matter connections to the striatum and

471   the IFC (Akkal et al., 2007, Nachev et al., 2008, Catani et al., 2012). All things being equal,

472   cortical connectivity between these regions may influence the effect of stimulation of the

473   preSMA on remote neural activity within the network. As discussed earlier, our results showed

474   that the suprathreshold preSMA TMS induced significant changes in the functional connectivity

475   between the preSMA and rIFCop, and between the rIFCop and the basal ganglia. Our DTI

476   results provided further evidence that the effect of the preSMA TMS on the network may be, in

477   part, attributable to the variability in the white-matter microstructure (i.e., FA and fiber length).

478   The fact that fiber length and FA values along the DTI fiber tracks between the right preSMA

479   and the rIFC were predictive of the SSRT and that fiber length was significantly correlated with

480   the task-free functional connectivity between the rIFCop and the basal ganglia, and with the

481   connectivity of the network as a whole indicates the behavioral relevance of these white-matter

482   pathways (also see King et al., 2012; Neubert et al., 2010; and Rae et al., 2015). These results

483   document individual differences in the white-matter microstructures (also see Behrman-Lay et

484   al., 2014) underlying the major pathways between the preSMA, rIFC, and the basal ganglia.

485   **However, it should be kept in mind the limitations of the DTI measures and DTI-based**

486   **tractography methods applied in the study (Thomas et al., 2014, Reveley et al., 2015),**

487   **particularly the crossing fiber issue that would likely influence the DTI tractography,**

488   **fiber counts, and FA measurements (Douaud et al., 2011). Future studies are needed to**

489   **further disentangle the relationships between functional and structural connectivity and**

490   **their relation to behavior.** We also cannot explain why the higher the FA values of the

491   preSMA ROI was correlated with less efficient stopping (Figure 5), while the opposite is true

492   with the FA values of the rIFC ROI. It is possible that the microstructure of the white matter

493   underlying the preSMA alone does not help the stopping performance as the preSMA is also

494   connected with the SMA proper which, in turn, highly connected with the motor cortex. It is

495   possible that for the stopping response, higher cross-talk between the preSMA and SMA may

496   impede rapid stopping of an already-initiated response. Future studies may further investigate

497   the relationship between structural connectivity and TMS-induced changes in functional

498   connectivity. The relationship between the structural and task-free functional connectivity is

499   also relevant to the understanding of functional deficiency after traumatic brain injury (TBI)

500   which has been shown susceptible to diffuse axonal injuries in the white matter (Johnson et al.,

501   2013).

502

503   This concurrent TMS-rfMRI study revealed a link between the right preSMA and its task-free

504   functional connectivity within the fronto-basal-ganglia network associated with rapid response

505   inhibition. The preSMA TMS not only induced a widespread activation within the stopping

506   network, but also modified the task-free functional connectivity within the network, particularly,

507   between the rIFCop and left striatum that was predictive of the efficiency of response inhibition.

508   The efficiency of response inhibition and functional connectivity of the network are also related

509   to individual differences in the white-matter microstructures. These results showed a complex

510   effect of preSMA TMS on the network activity, suggesting that the task-free functional and

511   structural connectivity between the rIFCop and basal ganglia are critical to the efficiency of

512   response inhibition.

513

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Captions

1. Figure 1a shows the localization of the TMS target (i.e., the right preSMA) and a schematic illustration of the timing of the single-pulse TMS relative to the EPI acquisition sequence during the scans. Single-pulse TMS was delivered 150 ms after the onset of the silence period (300 ms). The rfMRI scans were acquired using a gradient echo-planar-Imaging (EPI) sequence with a TR of 2000 ms and a scanner silence period of 300 ms at the end of each TR. Figure 1b shows the stop-signal task applied in the study. The stop-signal delay (SSD) was dynamically controlled such that it increased 50 ms for every successful stopping (stop-inhibit) response and decreased 50 ms for each failed-to-stop (stop-respond) response.

2. Figure 2 shows the results of the TMS-intensity induced BOLD signal change with a binary mask that included a priori ROIs of the fronto-basal-ganglia network. The top-left figure shows the ROIs. All reported voxels survived corrections for multiple comparisons using the topological false discovery rate (FDR) with a threshold of $p < 0.01$. Voxels showing significant differences between the low and high TMS conditions were extracted with an 8 mm diameter sphere centered on the peak of each cluster. SMA = supplementary motor area; rIFCop = right inferior-frontal cortex opercularis; rCaud = right caudate; rPal = right pallidum; rPut = right putamen; * = Scheffe's test, $p < .05$.

3. Figure 3 shows the results of linear regression analyses between the SSRT and the BOLD signal change (%) in the basal ganglia regions that also showed significant monotonic increase of TMS-intensity induced BOLD signal change. All the linear correlations between the SSRT

and the BOLD signal change in these regions were statistically significant ($p < .05$). Right
Pallidum (xyz): 16, 9 -5; Left Caudate (xyz): -16 26 3.

4. Figure 4 shows results of the analyses of functional connectivity. Figure 4a is a schematic
illustration of the functional connections included in the study and the functional connectivity
change (thicker lines) induced by the High TMS condition: right inferior-frontal cortex
opercularis (rIFCop), right striatum (rStri), left striatum (lStri), right pallidum (rPal), left pallidum
(lPal), and the subthalamic Nuclei (STN). Figure 4b shows: 1) the overall connectivity (all
connections combined) in the High TMS relative to the Low TMS condition; 2) TMS-induced
connectivity change in five connections: right preSMA – rIFCop, rIFCop – lStri, rIFCop – lPal,
rIFCop – rPal, and rIFCop - STN. The figures at the bottom show negative correlations
between the functional connectivity and the SSRT.

5. Figure 5 shows significant correlations between the white-mater microstructure (i.e., DTI
fiber length and FA values), functional connectivity, and the SSRT. Figure 5a shows the
relationship between the fiber length and the SSRT or task-free functional connectivity. Figure
5b shows the correlations between the FA values and the SSRT. The FA values were
extracted from the individual normalized FA maps (in the MNI space) in two regions (4 mm
diameter: ROI 1 [near right preSMA] = 12, 16, 50; ROI 2 [near rIFCop] = 30, 8, 22) centered on
the seed ROIs used in the tractography and the origin of the fiber tracks. The track map in the
figure was from a representative participant.