Focal disruption of temporal cortex in macaque during midbrain-induced neglect

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Summary

Hemi-spatial neglect in humans is a common aftermath of stroke damage to

subcortical and cortical brain structures, including the dorsocaudal temporal cortex. In

macaques, reversible inactivation of some homologous brain structures (e.g. midbrain,

prefrontal cortex) in selective attention tasks lead to behavioral symptoms of neglect,

but as yet there is no evidence linking temporal cortex to neglect. To identify the

neurological basis of neglect in macaques, we combined fMRI during attention tasks

with pharmacologic suppression of midbrain activity. Functional mapping of brain areas

during midbrain-induced neglect revealed a profound suppression of attention-related

modulation in a small region (aFST/IPa) on the floor of the superior temporal sulcus.

The same aFST/IPa region was also affected during neglect induced by inactivation of

the prefrontal cortex. These results identify for the first time a region in the temporal

cortex of macaque that is selectively affected during neglect induced by both subcortical

and cortical inactivation.

Keywords: spatial neglect, selective attention, superior colliculus, temporal cortex,

aFST/IPa region, fMRI, reversible inactivation, macaque

Introduction

In humans, hemi-spatial neglect is a common consequence of stroke damage to a range of cortical and subcortical structures (Corbetta and Shulman, 2011; Halligan et al., 2003; Heilman et al., 2000; Karnath and Rorden, 2012; Mesulam, 1981; Milner and McIntosh, 2005; Parton et al., 2004), and is defined as a behavioral syndrome characterized by failures to orient, detect or respond to stimuli in the visual field opposite to the brain lesion in the absence of sensory processing or motor deficits (Heilman et al., 1994; Rees et al., 2000). As such, hemi-spatial neglect is most closely associated with a disruption of attention-related mechanisms, that have been studied extensively in both humans and monkeys. Although neglect is diagnosed using clinical tests, performance deficits in attention-related paradigms such as the Posner cuing tasks are most sensitive during both acute and chronic stages (Rengachary et al., 2009).

The anatomy of spatial neglect is complex and entails the interaction between multiple brain systems. Spatial neglect is most commonly associated with damage to the inferior parietal and frontal cortices that have long been implicated in neglect (Bender and Butter, 1987; Critchley, 1953; Heilman and Valenstein, 1972; Husain and Kennard, 1996; Mort, 2003; Umarova et al., 2011; Verdon et al., 2010). At the same time, damage to subcortical structures in the telencephalon (e.g. striatum), thalamus (e.g. pulvinar) and midbrain (e.g. superior colliculus, SC) can lead to highly overlapping symptoms (Karnath et al., 2002; Snow et al., 2009; Weddell, 2004). Recent work in humans has placed emphasis on the temporal cortex, with meta-analysis suggesting that its contribution to spatial neglect has been previously under-appreciated (Karnath et

al., 2001). In particular, the dorsocaudal temporal cortex regions of the superior

temporal gyrus (STG) and temporo-parietal junction (TPJ) have been hypothesized to

play a particularly important role in spatial neglect (Chechlacz et al., 2010; Corbetta and

Shulman, 2002; Ellison, 2004; Friedrich et al., 1998; Hillis, 2005; Karnath, 2004; Meister

et al., 2006; Thiebaut de Schotten et al., 2005). These temporal cortical regions are also

part of the functional network with frontal and parietal areas implicated in spatial

attention in humans (Corbetta et al., 2005).

Understanding the brain mechanisms underlying spatial neglect requires

systematic testing of hypotheses in animal models such as the macaque, whose

perceptual specializations are similar to those in humans (Orban et al., 2004). Attention-

related deficits associated with visual neglect in humans have been demonstrated in the

macaque following reversible inactivation of several homologous brain structures, such

as the SC, pulvinar, parietal cortex (lateral intraparietal area, LIP) and prefrontal cortex

(frontal eye fields, FEF) (Gregoriou et al., 2014; Lovejoy and Krauzlis, 2010; Monosov et

al., 2011; Petersen et al., 1987; Wardak et al., 2004). However, the temporal cortical

regions functionally linked to spatial neglect are yet to be identified in monkeys (Patel et

al., 2015).

To determine brain regions functionally associated with spatial neglect in

monkeys, we performed fMRI before and during midbrain-induced neglect in two

monkeys performing visual selective attention tasks. We chose reversible inactivation of

midbrain SC to induce spatial neglect, because inactivation of this structure leads to

robust attention-related deficits, which are a hallmark of neglect (Lovejoy and Krauzlis,

2010; Zénon and Krauzlis, 2012). The broad coverage of fMRI provides a means to

compare attention-related modulation throughout the brain under normal behavior

("control") and following SC inactivation ("neglect") to identify brain regions functionally

affected during the induced neglect phenomenon.

Our results show that, across the brain, the strongest unilateral suppression of

attention-related modulation during midbrain-induced neglect was found in a

circumscribed region (aFST/IPa) of the mid-STS cortex. Smaller unilateral reductions in

modulation were observed in other regions of the cortex including FEF and part of area

TPO. Surprisingly, neglect induced by inactivation of the prefrontal cortex also affected

the same aFST/IPa region and additional experiments demonstrated that the reduction

in attention-related modulation of the aFST/IPa region during neglect was not contingent

on the stimulus feature used in the attention tasks. These findings identify for the first

time a region in the mid-STS cortex of macaque that is linked to hemi-spatial neglect

and is a functional component of both midbrain and prefrontal circuits associated with

selective attention.

Results

Two adult macaques were scanned using BOLD fMRI across repeated sessions

while performing three attention tasks. During some sessions, visual neglect was

induced through inactivation of the superior colliculus using injection of muscimol,

whereas during other sessions there was either no injection or the injection of a saline

control. During fMRI data collection, the Baseline, Ignore and Attend tasks were

presented in blocks (Fig. 1A-D; See Methods). In all three tasks, the color of the central

cue indicated the relevant stimulus to be monitored for change detection. The monkeys

maintained strict central fixation and reported the relevant changes detected by

releasing a joystick. In Baseline task, monkeys monitored the fixation stimulus to detect

a possible luminance change. The Ignore task was similar to the Baseline task but

included peripheral visual stimuli that could change motion direction but were entirely

task irrelevant. In the Attend task, monkeys monitored the same peripheral visual stimuli

to detect possible changes in motion direction. Both monkeys performed the three

attention tasks reliably, obtaining hit rates for relevant changes that were significantly

higher than false alarm rates on both trials with task-irrelevant changes and catch trials

containing no changes (Chi-square proportion test; $p<0.0001$).

Neglect induced by the suppression of midbrain activity

Spatial neglect was induced by reversible inactivation of the superior colliculus

(SC). Specifically, we injected $0.3 - 0.5$ μl of muscimol into the deep layers of SC (left

SC in monkey #1 and right SC in monkey #2). In addition to the neglect effects,

described below, inactivation affected the metrics of saccadic eye movements, including

changes in latency and peak eye velocity. These changes were a useful means to

monitor the location and duration of the muscimol effects on SC activity, as the saccadic

effects were retinotopic and affected only portions of the visual field (Fig. 1E). By

mapping the changes in saccade metrics caused by muscimol 30 minutes following the

end of injection, we were able to identify the specific portion of the visual field affected in

each session (blue region in Figure 1E) and confirm that the visual stimulus in the

attention tasks fully overlapped with the affected visual field (see Figure 1E, stimuli

depicted as white circles). Following the confirmation of SC inactivation, monkeys were

placed in the scanner for imaging in three attention tasks, which were always performed

while the animal maintained strict central fixation. The effectiveness of muscimol was

checked at the end of each imaging run (every 8 minutes) by having the monkeys

perform a pair of visually guided saccade into and out of the affected visual field

location, as illustrated for a sample session (Figure 1E, bottom); the difference in

latencies confirmed that the SC remained inactivated for the full duration of the imaging

runs in the experimental session. For every imaging session, the latencies of saccades

to targets into the affected field were significantly longer than the latencies of saccades

to targets in the unaffected visual field (Wilcoxon rank sum test; $p<0.05$).

Superior colliculus inactivation disrupted detection performance in the Attend

task for contralateral stimulus changes in both monkeys, in agreement with previous

findings (Lovejoy and Krauzlis, 2017; 2010; Zénon and Krauzlis, 2012). To quantify

these deficits, we compared the hit rate for motion-direction changes in the contralateral

visual field versus the ipsilateral visual field for each session (Fig. 1F). During SC

inactivation (blue symbols), all but one session showed a significant reduction in hit rate

for motion-direction changes for the stimulus in the affected contralateral visual field

compared to the stimulus in the unaffected ipsilateral visual field (Chi-square proportion

test; p<0.05). For the no-injection and saline sessions (orange and black symbols), we

did not find a significant difference in hit rates between the contralateral and ipsilateral

visual fields (Chi-square proportion test; p<0.05). These results show that SC

inactivation caused deficits in the detection of contralateral stimulus-change events,

akin to the deficits in the detection of contralateral targets observed in hemi-spatial

neglect (Corbetta et al., 2005; Rengachary et al., 2009). We refer to the deficits in the

Attend task during SC inactivation as *midbrain-induced neglect*.

Overall, we collected 18 sessions with muscimol injection (880 blocks each for

both the Ignore and Attend tasks in monkey #1, 912 blocks each for monkey #2), 16 no-

injection sessions (920 blocks each for both the Ignore and Attend tasks in monkey #1,

1008 blocks each for monkey #2), and 8 saline sessions in Monkey # 1 (928 blocks

each for both the Ignore and Attend tasks). Throughout the manuscript, we refer to the

no-injection sessions as "control" and the muscimol sessions as "neglect".

Midbrain-induced neglect linked to aFST/IPa region in the mid-STS cortex

Taking advantage of the broad coverage of fMRI, we measured the attention-

related modulation of brain activity with and without midbrain-induced neglect.

Comparing these conditions allowed us to identify the brain regions that were selectively

affected during neglect. Attention-related modulation was defined as the contrast

between the Attend and Ignore tasks. To minimize the contribution of saccadic eye

movements, rewards and joystick-related movements, regressors for these variables

were included as part of the general linear model (see Methods). We further excluded

voxels that mapped onto foveal locations, based on a separate retinotopic mapping

experiment (see Methods), because these might be subject to the very small stimulus

differences at the fovea in the two conditions (black versus red cue; Fig. 1B, C). The

rationale for this approach and a full map of attention-related modulation including

foveal voxels in the same attention tasks and animals were described in a previous

study (Bogadhi et al., 2018).

In the absence of SC inactivation during control sessions, the Attend blocks

elicited higher BOLD responses in several brain areas compared to the Ignore blocks.

For each monkey, the t-score maps showing this attention-related modulation

(Bonferroni corrected; $p < 0.05$) were projected onto partially inflated cortical surface of

the hemisphere ipsilateral to the pending SC inactivation (Fig. 2A, 2C, see Fig. S1 for

contralateral hemispheres). Consistent with previous work (Caspari et al., 2015;

Stemmann and Freiwald, 2016), we found significant modulation in areas MT, MST,

FST, PGa, IPa and parts of TEO and TPO of the superior temporal sulcus, areas LIPd,

LIPv and area PEa of the intraparietal sulcus, and areas 45b, 8Bs, 8Ad, 8Av, 46d, 46v

of the frontal cortex (Fig. 2A, 2C).

Following midbrain-induced neglect, certain cortical subregions of the injected

hemisphere showed reduced attention-related modulation (Fig. 2B, 2D). In both

monkeys, the reduction was strongest in a portion of the mid-STS. In monkey #2 there

was no significant reduction in attention-related modulation outside of this region (Fig.

2D), whereas in monkey #1, weaker but statistically significant reductions were also

observed in IPS and frontal cortex (Fig. 2B). There was no evidence of suppressed

attention-related modulation in the contralateral hemisphere, although there was some

evidence of enhanced attention-related modulation (see Supplementary Fig. S1,

discussed further below).

To visualize the suppression in attention-related modulation across the cortex

during neglect, we performed a voxel-wise ANOVA with two factors and two levels each

– Covert attention (Attend and Ignore conditions) and Neglect (control and neglect

sessions). The ANOVA was based on the Attend and Ignore BOLD measurements in

the control and neglect sessions (see Methods), with the interaction term capturing the

attention-related deficits associated with neglect. This analysis was similar to the

ANOVA analysis used in a previous fMRI study in humans investigating the neural basis

and recovery of spatial attention deficits in neglect (Corbetta et al., 2005).

Hemi-neglect is characterized by behavioral deficits contralateral to injury or

inactivation of SC as demonstrated in this study (Fig. 1F). Thus, in the present

experiments, the cortical areas most directly linked to midbrain-induced neglect would

be ipsilateral to the injection site and show a unilateral suppression of BOLD attention-

related modulation during neglect. To identify the brain regions whose attention-related

modulation was suppressed unilaterally during neglect, we overlaid the interaction term

F-statistic from the voxel-wise ANOVA onto partially inflated cortical surfaces of the

ipsilateral hemispheres in both monkeys (Fig. 3A, 3B). The negative sign of the F-

statistic reflects decrease in modulation during neglect (see Methods).

The inflated maps of F-statistic in both monkeys show one contiguous patch of

blue in the mid-STS cortex (Fig. 3A, 3B). The blue region shows voxels strongly

affected in the aFST/IPa region during neglect (Monkey #1: $F(1,24971) = -165.58$;

Monkey #2: F (1, 26645) = -111.59). The degrees of freedom (Monkey #1: 24971;

Monkey #2: 26645) indicate the BOLD measurements during the Attend and Ignore

blocks across all the control and neglect sessions. A magnified view of the STS shows a

large swathe of blue in the mid-STS region that reflects the spatial extent of the

reduction in attention-related modulation during neglect (Fig. 3C, 3D). The affected

voxels in the mid-STS spanned two anatomical areas – anterior FST and posterior IPa

in both monkeys (Fig. 3C, 3D), and hence we refer to this region as aFST/IPa.

We localized the effect in aFST/IPa region to the lower part of the fundus in STS

in both monkeys at the same anterior-posterior location as shown in coronal slices (Fig.

3E, 3F). We observed a significant increase in modulation on the contralateral side

during neglect in both monkeys (Monkey #1: F (1,24971) = 29.83; Monkey #2: F (1,

26645) = 44.15). The unilateral suppression of modulation in the aFST/IPa region (Fig.

3E, 3F) combined with the lateralized behavioral deficits observed during neglect (Fig.

1F) demonstrates a strong link between aFST/IPa region and midbrain-induced neglect.

Control analyses accounting for other factors such as saccadic eye movements,

rewards, and joystick related movements (see Supplemental Info, Fig. S2), as well as

comparisons with saline injection controls (see Supplemental Info, Fig. S3) further

confirm and strengthen our finding that the aFST/IPa region in mid-STS cortex was

strongly linked to midbrain-induced neglect.

Temporal and frontal cortical regions affected during midbrain-induced neglect

The aFST/IPa region ipsilateral to SC inactivation was the most affected brain

region during neglect both in terms of size and spatial extent of the effect, and hence

pops out in the inflated maps of the voxel-wise analysis (blue region in Fig. 3). In

comparison, the effect in ipsilateral frontal cortex (Monkey #1: $F_{(1,24971)} = -38.07$;

Monkey #2: $F_{(1, 26645)} = -40.51$) and MT (Monkey #1: $F_{(1,24971)} = -33.71$; Monkey

#2: $F_{(1, 26645)} = -50.87$) was significant but weaker in spatial extent and size, and

hence was not easily seen in the inflated maps of the voxel-wise analysis (Fig. 3). To

quantify the effect on attention-related modulation during midbrain-induced neglect in

different cortical regions, we performed regions of interest (ROIs) analysis and identified

the brain regions that showed unilateral reduction in attention-related modulation,

consistent with the lateralized behavioral deficits observed during neglect (Fig. 1F).

Regions of interest (ROIs) were defined as 2mm-radius spheres centered on the

local maxima of the attention-related modulation map from the control sessions; we

compared the modulation in these ROIs between the control and neglect sessions.

Ipsilateral ROIs were defined based on the modulation maps shown in Fig. 2A, 2C and

contralateral ROIs were defined based on the modulation maps shown in Fig. S1A,

S1C. In total, we found 9 cortical ROIs that showed modulation at overlapping or

identical anatomical locations in both the ipsilateral and contralateral hemispheres of

both monkeys.

The 9 cortical ROIs for the hemisphere ipsilateral to the SC inactivation are

illustrated in Fig. 4. The coronal slices show the anatomical location and attention-

related modulation during control and neglect (as in Fig. 2), and the time-courses

quantify the %change in BOLD for Attend and Ignore conditions during control and

neglect. For each ROI, we also computed d-prime values (which capture effects on both

the mean and variance of the BOLD signal) to summarize the attention-related

modulation during control and neglect; the mean attention-related modulations (d') and

bootstrapped confidence intervals for both ipsilateral and contralateral ROIs during

control and neglect are shown in the bar plots (Fig. 4). To identify the regions with

significant changes, we then compared the modulation (d') during control and neglect

for ipsilateral and contralateral ROIs (bootstrap test; $p < 0.05$). The rows in Fig. 4 present

the ROIs rank-ordered by the size of the unilateral effect on attention-related modulation

during midbrain-induced neglect.

Consistent with the voxel-wise ANOVA results (Fig. 3), we found significant

unilateral reductions in attention-related modulation across both monkeys in the

ipsilateral mid-STS ROIs – aFST/IPa and TPO (Fig. 4A, 4B). The effect was specific to

the hemisphere ipsilateral to SC inactivation – we did not find any reduction in

modulation of the contralateral aFST/IPa and TPO. On the contrary, we found an

increase in modulation of the contralateral aFST/IPa and TPO of monkey # 2, consistent

with the observation that monkey #2 showed a modest increase in performance (6.6 %)

for the ipsilateral stimulus in the Attend task (Fig. 1F). These results further strengthen

our finding that the mid-STS regions show unilateral suppression of modulation during

midbrain-induced neglect and highlight the strong link between mid-STS cortex and

neglect.

We also found regions with significant changes in the frontal and parietal cortex.

However, unilateral reduction in modulation was observed only in FEF. In the prefrontal

cortex, FEF showed significant reduction in modulation ipsilateral to SC inactivation in

both monkeys with no significant effect on the contralateral side (Fig. 4C). Another ROI

in the prefrontal cortex showed a significant effect only in one monkey: there was a

significant reduction in modulation of ipsilateral and contralateral vlPFC in monkey #1

but not in monkey #2 (Fig. 4D). In the parietal cortex, we found significant reduction in

ipsilateral LIPd of both monkeys and contralateral LIPd of monkey #2 (Fig. 4E). In

monkey #2, both ipsilateral and contralateral effects in LIPd were of equal magnitude,

with no significant effect in LIPv (Fig. 4F).

There were also some changes in visual areas but the effects were not unilateral

and were mixed across both monkeys. In ipsilateral MT, both monkeys showed

significant reduction in modulation (Fig. 4G). However, we also found a significant but

modest reduction in contralateral MT that was smaller compared to the reduction in

ipsilateral MT. In V2v, both monkeys showed significant reductions in the ipsilateral

ROI. However, Monkey #1 also showed a significant and larger reduction in

contralateral V2v (Fig. 4H). In visual cortical ROI V1, we found a significant reduction in

modulation ipsilateral to SC inactivation in one monkey (Fig. 4I).

Control analyses comparing attention-related modulation in different ROIs during

neglect and saline sessions (see Supplemental Info, Fig. S4) further confirm that the

temporal cortical regions – aFST/IPa and TPO, along with FEF in the prefrontal cortex

showed a unilateral reduction in modulation during midbrain-induced neglect. We also

verified that these findings were robust to the attention-related measure (d') we used by

computing another attention-related measure that is equivalent to the β coefficient of the

term contrasting Attend and Ignore conditions – namely, the difference between mean

BOLD in Attend and mean BOLD in Ignore ($\mu_A - \mu_I$). These findings taken together with

the results from the voxel-wise analysis implicate for the first time a region in the

macaque temporal cortex in visual hemi-neglect, in this case induced through

inactivation of the SC.

Effect in aFST/IPa region during neglect was not contingent on visual motion

A possible explanation for the reduction of attention-related modulation in the

aFST/IPa region of macaque temporal cortex during midbrain-induced neglect is that

the aFST/IPa region is related to higher-order motion processing. This explanation is

partially consistent with previous fMRI reports showing activations related to higher-

order motion processing and object-related processing in similar parts of the mid-STS

cortex (Nelissen et al., 2006). To test if the effect in the aFST/IPa region during neglect

was contingent on visual motion, we performed fMRI in similar attention tasks with and

without SC inactivation in monkey #1 using a non-motion stimulus. All the attention

tasks were the same as before, except that the motion stimuli were replaced with white

noise stimuli and motion-change detection was replaced with a second-order orientation

detection (see Methods). In the Ignore task, the monkey monitored the fixation stimulus

for a luminance-change and ignored the peripheral white noise distractor stimuli and the

brief second-order (i.e., defined by contrast not luminance) orientation pulse (Fig. 5A).

In the Attend task, the monkey monitored the peripheral white noise stimuli and

detected the brief second-order orientation pulse (Fig. 5B). The SC inactivation and

other methods were the same as described for the motion stimuli experiments (Fig. 1).

We confirmed that SC inactivation significantly affected performance for the

contralateral second-order orientation changes compared to the ipsilateral second-order

orientation changes in the Attend task during all sessions (Fig. 5C; Chi-square

proportion test; p<0.05). We collected 7 no-injection (824 blocks each for both the

Ignore and Attend tasks) and 9 SC inactivation sessions (848 blocks each for both the

Ignore and Attend tasks) which we refer to as control and midbrain-induced neglect

sessions, respectively.

First, we determined if the aFST/IPa region showed attention-related modulation

in the absence of visual motion by contrasting Attend and Ignore tasks in the control

sessions (Bonferroni corrected; p<0.05). We found significant attention-related

modulation in the aFST/IPa region (see black arrow in Fig. 5D), in addition to areas of

posterior STS, IPS and the frontal cortex. The attention-related modulation in the

second-order orientation task was sparser compared to that in the motion-change

detection task, perhaps because the orientation stimulus lacked the continuous dynamic

changes of the motion stimulus. These results show that the aFST/IPa region was

modulated during covert visual attention even in the absence of visual motion.

Second, we determined if the attention-related modulation in aFST/IPa during the

second-order orientation task was also changed during midbrain-induced neglect (Fig.

5E), using the same voxel-wise ANOVA analysis described in the earlier section. The

inflated map of the interaction term F-statistic in the ipsilateral STS of monkey #1

showed that the voxels most affected during neglect were once again identified in the

mid-STS region at the border between anterior FST and posterior IPa (F (1, 23083) = -

63.64; see white arrow in Fig. 5F). On the contrary, there was no effect in the

contralateral mid-STS region during neglect (F (1, 23083) = 0.000419). Importantly, the

affected voxels in the mid-STS (blue region in Fig. 5F) completely overlapped with the

aFST/IPa region that was affected in the motion task (white contour in Fig. 5F). In fact,

further localization of the affected voxels revealed the same lower part of the fundus in

STS at the identical anterior-posterior location (compare Fig. 5G and Fig. 3E). These

results show that the same voxels in the aFST/IPa region were affected during neglect

in both the motion and second-order orientation tasks, demonstrating that the effect in

aFST/IPa region during midbrain-induced neglect was not contingent on visual motion.

The same aFST/IPa region was affected during neglect induced by FEF inactivation

Is the selective involvement of the aFST/IPa region specific for midbrain-induced

neglect, or would cortically induced neglect similarly reduce attention-related modulation

in this mid-STS region? To address this, we inactivated the frontal eye fields (FEF) of

the prefrontal cortex in separate experiments. Like the SC, FEF inactivation in

macaques has previously been shown to lead to performance deficits akin to spatial

neglect (Gregoriou et al., 2014; Monosov et al., 2011). We identified FEF in the anterior

bank of the arcuate sulcus using microstimulation with currents of 40 μA to evoke

saccades (Fig. 6A). For reversible inactivation, we injected 1-2 μl of muscimol and

mapped the affected visual field using a visually guided saccade task (see Methods;

Fig. 6B). The contralateral stimulus in the attention task (white circle) fully overlapped

the portion of the visual field showing saccade deficits during FEF inactivation (blue

region). We also confirmed that the muscimol effect lasted throughout the entire

imaging session using the same methodology as described for SC inactivation and

imaging (see Methods).

Perceptual choices in the Attend task for contralateral motion-changes compared

to ipsilateral motion-changes were not significantly affected during FEF inactivation.

However, we did find a significant effect on the median response times for contralateral

motion-changes compared to ipsilateral motion-changes (median RT_{contra} = 545 ms;

RT_{ipsi} = 521 ms; Wilcoxon rank sum test; p<0.001). A similar comparison of median

response times during control sessions did not show any significant effect (median

RT_{contra} = 523 ms; RT_{ipsi} = 523 ms; Wilcoxon rank sum test; p=0.92). These results

confirmed that prefrontal cortex causally affects performance in attention tasks akin to

spatial neglect. Over all, we collected 7 no-injection (768 blocks each for both the Ignore

and Attend tasks) and 7 inactivation sessions (736 blocks each for both the Ignore and

Attend tasks), which we refer to as control and FEF-induced neglect sessions,

respectively.

Before determining if aFST/IPa region was affected during FEF-induced neglect,

we confirmed that the aFST/IPa region (see black arrow in Fig. 6C) showed significant

attention-related modulation during control sessions in addition to other regions of STS,

IPS, AS and PS (Fig. 6C), in agreement with the attention-related modulations observed

previously in the same task (Fig. 2C). To determine the effect of FEF-induced neglect

on the attention-related modulation throughout cortex (Fig. 6D), we performed the same

voxel-wise ANOVA analysis as described in earlier section and the F-statistic of the

interaction term for voxels in the ipsilateral STS is shown on the inflated cortical surface

in Fig. 6D.

The voxels most affected during FEF-induced neglect were again found in the

ipsilateral mid-STS region at the border between anterior FST and IPa ($F_{(1, 21322)}$ = -

93; white arrow in Fig. 6E), with no significant effect in the contralateral mid-STS region

($F_{(1, 21322)}$ = 2.684). The affected region during FEF-induced neglect (blue region)

fully overlapped with the affected region during midbrain-induced neglect (white

contour). Further localization showed the affected region to be in the fundus of STS at a

similar anterior-posterior location (compare Fig. 6F and Fig. 3F). These results show

that the aFST/IPa region was affected not only during midbrain-induced neglect but also

during neglect induced by FEF inactivation.

The effect in aFST/IPa region during FEF inactivation was weaker compared to

the effect in aFST/IPa during SC inactivation (compare Fig. 3D and Fig. 6E). We

suspect this was likely because of the difference in performance deficits in the attention

tasks during FEF and SC inactivations. SC inactivation resulted in significant

performance deficits whereas FEF inactivation yielded modest but significant reaction

time effects. A stronger inactivation of FEF with a higher volume of muscimol might

have yielded comparable deficits to SC inactivation. Regardless of the size of the effect

in aFST/IPa during FEF inactivation, our results show that the aFST/IPa region was

affected during neglect induced by both cortical and subcortical inactivation.

Discussion

In humans, the anatomy of hemi-spatial neglect includes regions of the superior

temporal cortex that are part of a network with frontal and parietal cortex and subcortical

brain structures (Corbetta et al., 2005; Hillis, 2005; Karnath et al., 2005). However,

temporal cortical regions linked to spatial neglect have not yet been identified in

monkeys. In this study, we combined fMRI with and without hemi-spatial neglect

induced by reversible inactivation of superior colliculus in monkeys performing a covert

attention task and identified the strongest reduction in attention-related modulation

during midbrain-induced neglect in the temporal cortex. Specifically, a contiguous

cluster of voxels in the ipsilateral aFST/IPa region of the mid-STS showed a dramatic

reduction in attention-related modulation during neglect, and this effect was not

contingent on stimulus motion. Moreover, this reduction was accompanied by a modest

but significant increase in the contralateral aFST/IPa region. In comparison, smaller

unilateral reductions in modulation were observed in other ipsilateral regions of the

cortex including FEF and part of area TPO. These findings, taken together with the

performance deficits during neglect, demonstrate for the first time in monkeys a strong

link between modulation in the mid-STS region of the temporal cortex and attention-

related deficits associated with neglect.

Possible pathways from superior colliculus to mid-STS cortex

How does suppression of activity in superior colliculus have such a profound

influence on the modulation in the aFST/IPa region of the mid-STS cortex? Among

several tectofugal pathways (Benevento and Fallon, 1975; Partlow et al., 1977), we

speculate two possible pathways through thalamus as the likely candidates for

mediating these effects. The first is the pathway from the intermediate and deep layers

of SC to medial pulvinar and the reciprocal connections between medial pulvinar and

regions of the mid-STS cortex (Benevento and Standage, 1983; Burton and Jones,

1976; Yeterian and Pandya, 1989). The second is the pathway from the intermediate

and deep layers of SC to FEF through mediodorsal thalamus (Benevento and Fallon,

1975), and FEF projections to regions of the mid-STS cortex (Stanton et al., 1995). The

dramatic reduction in modulation in the aFST/IPa region compared to the FEF during

midbrain-induced neglect suggests that the pathway through the medial pulvinar might

have larger influence on the aFST/IPa region compared to the pathway through FEF.

Priority maps in the subcortical and cortical areas causally affect the aFST/IPa region

Superior colliculus activity represents spatial "priority maps" and suppression of

this activity leads to robust performance deficits in attention tasks akin to neglect

(Fecteau and Munoz, 2006; Lovejoy and Krauzlis, 2010). In addition to the SC,

prefrontal cortex (FEF) is another brain structure that represents spatial "priority maps"

and suppression of activity in FEF also leads to performance deficits akin to spatial

neglect (Gregoriou et al., 2014; Monosov et al., 2011). Our results showed that

attention-related BOLD modulation in the same aFST/IPa region was reduced when

activity in SC or FEF was suppressed, demonstrating that these subcortical and cortical

"priority maps" causally influence the aFST/IPa region. This finding is in agreement with

previous fMRI reports that similar mid-STS regions are causally affected by

manipulations in frontal and parietal areas FEF and LIP (Ekstrom et al., 2008; Wilke et

al., 2012). In addition, these mid-STS regions are reciprocally connected with the dorsal

and ventral stream areas. These results taken together with previous anatomical

evidence suggest that the mid-STS regions (aFST/IPa and TPO) may combine spatial

"priority maps" from the sensorimotor structures (SC, FEF, LIP) with the visual

information from the dorsal and ventral stream areas (Boussaoud et al., 1990; Saleem

et al., 2000).

aFST/IPa region: a potential homolog of the human temporoparietal junction?

In humans, temporal cortical regions including the temporoparietal junction (TPJ)

and its neighboring superior temporal cortical areas play a crucial role in spatial neglect

(Corbetta and Shulman, 2011; Karnath and Rorden, 2012), and are functionally

connected to frontal and parietal areas (Corbetta et al., 2005). In macaques, similar

mid-STS regions as identified in this study are functionally connected to the

sensorimotor structures (SC, FEF, LIP) implicated in spatial attention and neglect

(Ekstrom et al., 2008; Wilke et al., 2012). This functional dependence on sensorimotor

structures raises an interesting possibility that these mid-STS regions in macaque are

homologous to the areas of the superior temporal cortex associated with spatial neglect

in the human. At the same time, a recent study comparing humans and monkeys in an

attention task was unable to identify a functional homologue of TPJ in the macaque, and

thus concluded the opposite – that the human TPJ likely evolved independently and is

not a shared primate feature (Patel et al., 2015). Importantly, the authors suggested that

the macaque might not be an adequate animal model to study mechanisms of spatial

attention and neglect. Here, by demonstrating a prominent and focal area in the mid-

STS region that is affected during neglect induced by both cortical and subcortical

inactivation, our findings suggest the TPJ region in humans has a potential homologue

in the macaques. Beyond the location in the temporal cortex, the causal dependence of

the mid-STS region on activity in sensorimotor spatial "priority maps" (SC, FEF) is

similar to the proposed link between temporal cortical regions of the ventral attention

network and sensorimotor areas of the dorsal attention network in human neglect

(Corbetta and Shulman, 2011). While homology is notoriously difficult to establish, these

findings for the first time establish a functional link between the temporal cortex and

hemi-spatial neglect in the macaque and offers a new bridge between human and

nonhuman primate models of hemi-spatial neglect.

aFST/IPa region could be polysensory and may play a role in target detection

As far as we know, there is no electrophysiology data available to infer function

from the properties of neurons in the aFST/IPa region we identified, although there is

fMRI evidence that similar parts of the STS show motion-sensitivity as well as object-

selectivity (Nelissen et al., 2006). Inspection of the electrophysiology literature for the

neighboring cortical areas suggests that the aFST/IPa region closely corresponds to the

middle part of the superior temporal polysensory (STP) region (Scalaidhe et al., 1995),

and visual activity of neurons in the STP region depend on striate cortex and midbrain

SC (Bruce et al., 1986). These previous findings taken together with our result that

modulation in aFST/IPa region depends on midbrain activity suggest that the aFST/IPa

region is likely to be a part of the STP region. Neurons in the caudal and rostral parts of

the STP region respond to visual, auditory and somesthetic stimuli and exhibit not only

unimodal but also bimodal and trimodal response properties (Bruce et al., 1981;

Hikosaka et al., 1988). Neurons in the anterior (rostral) STP region are also selective for

3D structure from motion (Anderson and Siegel, 2005), similar to neurons in the middle

part of area FST (Mysore et al., 2010). Importantly, STP lesions result in delayed

detection of contralateral targets (Scalaidhe et al., 1995), and lesions in the dorsal bank

and fundus of STS result in unilateral neglect (Luh et al., 1986; Watson et al., 1994).

These observations from the overlapping and neighboring regions suggest that the

aFST/IPa region is likely part of the previously described STP region that contains cells

responsive to multi-modal stimulation and may play a role in target detection.

Conclusion

Using fMRI and reversible inactivation in monkeys performing attention tasks, we

identified a novel brain region in the mid-STS cortex (aFST/IPa) to be the most affected

brain region during neglect induced by subcortical and cortical inactivation, and we

showed that this effect is not contingent on the specific visual feature used in the

attention tasks. Our results demonstrate for the first time in monkeys a functional link

between temporal cortex and neglect, thereby bridging the gap between human and

macaque model of hemi-spatial neglect. Future experiments in the aFST/IPa region

should address the neuronal responses and their modulation, at different epochs in the

selective attention tasks, both before and during neglect, to better understand the

functional link between aFST/IPa neuronal activity and neglect. Such experiments might

also provide insights into why loss of activity from the midbrain SC, an evolutionarily

ancient structure important for orienting movements, appears to especially affect this

particular region of primate visual cortex, amongst the many neocortical areas that

could have been affected.

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Author Contributions

All authors designed the experiments. A.R.B. and A.B. conducted experiments and

collected the data. A.R.B. analyzed the data. All authors interpreted the results. A.R.B.

and R.J.K wrote the manuscript.

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 Figure Legends

Figure 1. Behavioral tasks and midbrain-induced neglect (SC inactivation)

A) In the Baseline task, a black square around the central fixation spot instructed the

monkey to monitor the fixation stimulus and detect luminance-change during a delay

period of 1 – 3 seconds.

B) In the Ignore task, a black square around the central fixation spot instructed the

monkey to monitor the fixation stimulus in the presence of peripheral motion distractors

and detect luminance-change during a delay period of 1 – 3 seconds. Independent of

the fixation spot dimming, one of the motion stimuli changed direction which the monkey

ignored as part of the task.

C) In the Attend task, a red square around the central fixation spot instructed the

monkey to monitor both the peripheral motion stimuli and detect a possible motion

direction-change that occurred in one of the motion stimuli during a delay period of 1 – 3

seconds. The central fixation spot did not dim during Attend condition. In all tasks, the

monkey reported the relevant change by releasing the joystick within 0.8 s for a juice

reward.

D) Timeline of an example SC inactivation session and imaging. The session began

with reversible inactivation of SC outside the scanner. In the scanner, the monkey

performed all three tasks presented in a block design during an imaging run that lasted

8 minutes (black bars). At the end of each imaging run, the monkey performed visual

guided saccades to targets in the affected and unaffected visual fields (grey bars). An

average of 14 imaging runs were collected in an inactivation session.

E) The visual field map shows the effect of SC inactivation on the peak velocity of the

saccades to targets in the visually guided saccade task (top panel). The blue region

indicates the affected part of the visual field. Black dots indicate the retinotopic position

of the saccade targets. The white circles indicate the positions of the motion stimuli in

the Ignore and Attend tasks. The time course of muscimol effect was measured in the

scanner using visual guided saccade task at the end of each imaging run (bottom

panel). Blue dots indicate the latencies of saccades to targets in the affected visual field

and green dots indicate the latencies of saccades to targets in the unaffected visual

field. μ and σ indicate mean and standard deviation respectively.

F) Performance in Attend task is shown for control (green), neglect (SC inactivation;

blue) and saline (black) sessions in both monkeys. % Hit rate for motion changes in the

affected visual field (y-axis) is plotted against % hit rate for motion changes in the

unaffected visual field (x-axis). Each data point represents a single session and error

bars indicate 95% CI.

Figure 2. Cortical maps of attention-related modulation in control and neglect (SC

inactivation) sessions

T-scores contrasting Attend and Ignore tasks were projected onto inflated cortical

surfaces of D99 in each monkey's native space along with anatomical boundaries (black

contours).

(A, B) Inflated cortical maps of t-scores show attention-related modulation in ipsilateral

(left) hemisphere of monkey # 1 during control (A) and neglect (B). The maps were

thresholded during control sessions (A) and the modulation for the same voxels is

shown during the neglect sessions (B).

(C, D) Same conventions as (A, B) but for monkey # 2.

See also Figure S1.

Figure 3. Midbrain-induced neglect linked to aFST/IPa region

(A, B) Inflated cortical maps of interaction term F-statistic show voxels whose

modulation was affected during neglect in the ipsilateral hemisphere of monkey # 1 (A)

and monkey # 2 (B). The effect during neglect is shown for the same voxels that

showed significant modulation during control sessions (Fig. 2A, 2C). The blue color

indicates voxels whose modulation was reduced the most during neglect and the green

colors indicate voxels with no reduction in modulation. The white contour indicates the

contiguous cluster of affected voxels in aFST/IPa region.

(C, D) Magnified versions of Fig. 4A and 4B highlighting the most affected mid-STS

aFST/IPa region during neglect in monkey # 1 (C) and monkey # 2 (D).

(E, F) Coronal slices show the anatomical locations of the affected aFST/IPa region in

monkey # 1 (E) and monkey # 2 (F). The white cross-hairs indicate the peaks of the

aFST/IPa ROI from Fig. 4A.

See also Figures S2, S3.

Figure 4. Effect of midbrain-induced neglect (SC inactivation) on the attention-

related modulation in cortical ROIs

(A – I) The name of the ROI is shown at the top-left of each row. Each row shows

coronal slices containing the peak of the ROI for both monkeys (Monkey # 1: Left

column; Monkey # 2: Right column). The coronal slices overlaid with attention-related

modulation during control and neglect (SC inactivation) sessions are shown next to

each other for comparison (as in Fig. 2). The location of the white cross-hair in each

coronal slice indicates the peak of the ROI in the hemisphere ipsilateral to the SC

inactivation site. Note that the peak of the ROI was identified based on the attention-

related modulation during control. The location of the coronal slice w.r.t the inter-aural

axis is shown on top of each coronal slice. Next to the coronal slices, mean BOLD time-

courses for the ipsilateral ROI are plotted as % change in BOLD on y-axis against

repetition time (TR) on the x-axis for the Attend (filled circles) and Ignore (open circles)

tasks performed during control (orange) and neglect (blue) sessions. TR = 0 on x-axis

indicates start of the block. The bar plot shows the attention-related modulation in the

ipsilateral ROI measured as d' during control (orange) and neglect (blue) sessions. For

comparison, the same measure is shown for the corresponding contralateral ROI during

control and neglect sessions. Error bars indicate bootstrapped 95% CI and ∗ indicates

statistical significance at 5% (p < 0.05). aFST refers to anterior part of anatomical area

FST. See also Figure S4.

Figure 5. Effect in aFST/IPa region during neglect was not contingent on visual

motion

(A, B) Same conventions as Fig. 1B, 1C except that peripheral motion stimuli were

replaced by white noise distractors and the motion-change event was replaced by a

brief (0.5 s) second-order orientation pulse.

C) Performance in the Attend task is shown for control (green) and neglect (blue)

sessions in monkey # 1. Hit rate (%) for orientation pulse in the affected visual field (y-

axis) is plotted against hit rate for orientation pulse in the unaffected visual field (x-axis).

Each data point represents a single session and error bars indicate 95% CI.

(D, E) Inflated cortical maps of t-scores contrasting the Attend (Fig. 5B) and Ignore (Fig.

5A) tasks show attention-related modulation in the ipsilateral (left) hemisphere of

monkey # 1 during control (D) and neglect (E) sessions. The black arrow points to the

modulation in aFST/IPa region during control (D). The maps were thresholded during

control sessions (D) and the modulation for the same voxels is shown during the neglect

sessions (E).

F) Magnified version of the inflated cortical map of the interaction term F-statistic shows

the changes in attention-related modulation during neglect in ipsilateral STS regions

including aFST/IPa of monkey # 1 in the second-order orientation task. The effect

during neglect is shown for the same voxels that showed significant modulation during

control sessions (Fig. 5D). The blue color indicates voxels whose modulation was

reduced the most during neglect and the green colors indicate voxels with no reduction

in modulation. The white contour indicates the aFST/IPa region affected during neglect

in the motion task and is the same as shown in Fig. 3C.

G) Coronal slice displays the anatomical location of affected aFST/IPa region in monkey

1 in the second-order orientation task. The white cross-hair indicates voxel with peak

attention-related modulation in aFST/IPa region during control.

Figure 6. The same aFST/IPa region was affected during FEF-induced neglect

A) Coronal section shows the localization of FEF in the anterior bank of arcuate sulcus

and illustrates two sample sites (red circles) at which electrical stimulation (70 ms train

duration, 350 Hz, biphasic pulses with duration of 0.3 ms, 40 μA) evoked saccadic eye

movements with directions and amplitudes (indicated by the trajectories in each of the

two corresponding panels) that depended on the location within the FEF. White stripes

in upper right of the MRI were produced by the contrast agent placed in the FEF

recording grid and the superimposed yellow line indicate the estimated electrode and

injectrode paths.

B) The visual field map shows the affected visual field (blue region) during FEF

inactivation. Same conventions as Fig. 1E (top panel).

(C, D) Inflated cortical maps of t-scores contrasting the Attend (Fig. 1C) and Ignore (Fig.

1B) tasks show attention-related modulation in the ipsilateral (right) hemisphere of

monkey # 2 during control (C) and neglect (D) sessions. The black arrow points to the

modulation in aFST/IPa region during control (C). The maps were thresholded during

control sessions (C) and the modulation for the same voxels is shown during the neglect

sessions (D).

E) Magnified version of the inflated cortical map of the interaction term F-statistic shows

the changes in attention-related modulation during FEF-induced neglect in ipsilateral

STS regions including aFST/IPa of monkey # 2 in the motion task. The effect during

neglect is shown for the same voxels that showed significant modulation during control

sessions (Fig. 6C). The blue color indicates voxels whose modulation was reduced the

most during neglect and the green colors indicate voxels with no reduction in

modulation. The white contour indicates the aFST/IPa region affected during midbrain-

induced neglect (SC inactivation) in motion task and is the same as shown in Fig. 3D.

F) Coronal slice shows the anatomical location of the affected aFST/IPa region during

FEF inactivation in monkey # 1. The white cross-hair indicates voxel with peak

attention-related modulation in aFST/IPa region during control sessions.

Methods

Animals

Two adult male rhesus monkeys (*Macaca mulatta*) weighing 7-9 kg participated

in this study. All experimental protocols were approved by the National Eye Institute

Animal Care and Use Committee and all procedures were performed in accordance with

the United States Public Health Service policy on the humane care and use of

laboratory animals. Under isoflurane and aseptic conditions, we surgically implanted

plastic head-posts and electrophysiology chambers to access the SC and FEF. The SC

chamber was angled 38° to the posterior of vertical and directed at the midline, 15 mm

above and 1 mm posterior to the interaural line. The FEF chamber was angled 30°

lateral of vertical and aimed at a point 18 mm lateral from the midline, 25 mm anterior to

the interaural line.

Experimental apparatus

Monkeys were seated and head-fixed in a custom-built MR-safe chair with a

joystick attached inside the chair. Before each imaging session, monkeys performed a

visual guided saccade task inside a darkened booth. The saccade task was controlled

using a modified version of PLDAPS (Eastman and Huk, 2012). Animals viewed visual

stimuli from a distance of 48 cm that were displayed at 1920 x 1200 resolution (~ 60° x

38°) and 100Hz frame-rate on a VIEWPixx display (VPixx Technologies, Saint-Bruno,

QC Canada), controlled by a mid-2010 Mac Pro (Apple Inc., Cupertino, CA) running

MATLAB (The Mathworks, Natick, MA) with the Psychophysics Toolbox extensions

(Brainard, 1997; Kleiner et al., 2007; Pelli, 1997). Eye position was recorded using an

EyeLink 1000 infrared eye-tracking system (SR Research Ltd., Ottowa, Ontario,

Canada).

During each imaging session, monkeys performed attention tasks and visual

guided saccade task inside the vertical scanner. Stimuli were back projected on to a

screen placed inside the bore of the vertical scanner using an Epson projector

controlled by a Windows 2007 machine running MATLAB R2012b (The Mathworks) with

the psychophysics toolbox extensions (Brainard, 1997). The timing of the stimuli and

events were controlled by a QNX system running QPCS. Monkey viewed the screen

through a mirror placed in front at a 45° angle. The total viewing distance of the screen

was 53 cm. Eye movements were acquired and monitored in the scanner using an

iView system (Version 2.4, SensoMotoric Instruments). Eye signal was calibrated at the

beginning of each session. Joystick presses and releases were detected by disruption

of an optic-fiber transmission using a custom-built device. Joystick was calibrated once

at the beginning of the experiments.

Attention tasks: Motion-change detection

In the scanner, both monkeys performed three behavioral tasks: Baseline, Ignore

and Attend. In all tasks, monkeys initiated the trial by holding the joystick down and

fixating the central fixation spot with a colored central cue on a grey background.

Monkeys fixated for the entire duration of the trial with in a 2° fixation window. The color

of the central cue indicated the trial condition. In Baseline and Ignore trials, the color of

the central cue was black (Fig. 1A, 1B) and the relevant stimulus was the fixation

stimulus. In Attend trials, the color of the central cue was red (Fig. 1C) and the relevant

stimulus was the peripheral motion stimulus. The sequence of events in three different

trial conditions are as follows.

In Baseline trials, following 0.5 s of fixation, the luminance of the fixation spot

decreased during a variable delay of 1 – 3 s on the 65% of the trials. Monkeys reported

the luminance change by releasing the joystick within 0.3 - 0.8 s to get a juice reward

(Fig. 1A). A total of 8401 trails (4433 in Monkey #1 and 3968 in Monkey #2) were

collected during control and 7484 trails (3667 in Monkey #1 and 3817 in Monkey #2)

were collected during SC inactivation in both monkeys. We also collected 4446 trials

during saline injection in monkey #1.

In Ignore trials, following 0.5 s of fixation, two random dot motion stimuli were

presented on either side of fixation at 8° eccentricity (radius) and 10° above horizontal

meridian (azimuth). During the variable delay of 1 – 3 s, the luminance of the fixation

spot decreased on 65% of the trials. Independent of the fixation luminance change, one

of the peripheral motion stimulus changed direction during the variable delay of 1 – 3 s

on the 65% of the trials. Monkeys ignored the motion direction change and reported the

luminance change by releasing the joystick within 0.3 - 0.8 s to get a juice reward (Fig.

1C). If the monkeys released the joystick for a motion direction change, the trial was

aborted. A total of 9139 trails (4912 in Monkey #1 and 4227 in Monkey #2) were

collected during control and 8240 trails (4083 in Monkey #1 and 4157 in Monkey #2)

were collected during SC inactivation in both monkeys. We also collected 4913 trials

during saline injection in monkey #1.

In Attend trials, following 0.5 s of fixation, two random dot motion stimuli were

presented at the same stimulus location as in Ignore trials. One of the peripheral motion

stimulus changed direction during the variable delay of 1 – 3 s on the 65% of the trials.

Monkeys reported the motion-direction change by releasing the joystick within 0.3 - 0.8

s to get a juice reward (Fig. 1E). There was no fixation luminance change in Attend

trials. A total of 8672 trails (4765 in Monkey #1 and 3907 in Monkey #2) were collected

during control and 7742 trails (4026 in Monkey #1 and 3716 in Monkey #2) were

collected during SC inactivation in both monkeys. We also collected 4794 trials during

saline injection in monkey #1.

In all tasks, 35% of the trials were catch trials and monkeys hold the joystick

down to get a juice reward.

Random dot motion stimuli

The random dot motion stimuli were circular patches of moving dots, with the

direction of motion of each dot drawn from a normal distribution with a mean value

(defined as the patch motion direction) at 30° above horizontal and a 16° standard

deviation. The lifetime (10 frames, 100 ms), density (25 dots/^{o2}/s), and speed of the dots

(15 °/s) were held constant. The radius of the aperture was set to 3°. Luminance of each

moving dot in the motion patches was 50 cd/m^2. The change in direction of motion (Δ)

was 1 ± 0.25 standard deviations for both monkeys across sessions.

1004

1005   *Fixation spot stimulus*

1006   The size of the fixation spot was 0.23º and the size of the central cue was 0.35º.

1007   The background luminance of the screen was 14 cd/m^2 and the luminance of the

1008   fixation spot was 50 cd/m^2. The luminance change in fixation spot during Baseline and

1009   FA trials was 1-2 cd/m^2 across sessions for both monkeys.

1010

Attention tasks: Orientation-pulse detection

In addition to the motion-change detection task, monkey # 1 also performed a

version of the attention tasks with orientation pulse stimuli instead of the random dot

motion stimuli. The sequence of events in all three conditions (Baseline, Ignore, Attend)

was kept the same as the motion-change detection version of the task. The onset of the

motion stimuli was replaced with the onset of white noise stimuli, and the motion-

direction change was replaced with a 0.5 s second-order orientation pulse (Fig. 5A, 5B).

In the Attend condition, the monkey reported the orientation pulse by releasing the

joystick within 0.3 - 0.8 s to get a juice reward (Fig. 5A), whereas in the Ignore condition,

monkey ignored the orientation pulse and reported the luminance change in the fixation

spot by releasing the joystick within 0.3 - 0.8 s to get a juice reward (Fig. 5B). In the

Attend condition, a total of 3700 trails were collected during control and 2680 trails were

collected during SC inactivation. In the Ignore condition, a total of 3752 trails were

collected during control and 2698 trails were collected during SC inactivation.

The second-order orientation stimulus was generated by briefly (0.5 s)

modulating the contrast of a white noise stimulus with a 2-dimensional sinusoid. The

noise stimulus was 6^0 in diameter and consisted of checks each the size of a pixel with

luminance values ranging from 8 – 84 cd/m^2, and the 2-dimensional sinusoid had a

spatial frequency of 0.7 cycles/deg, and its orientation was 90^0. We refer to this as a

second-order orientation stimulus, because the oriented grating briefly visible in the

stimulus was due to the local differences in contrast, not luminance differences. The

mean luminance (38 cd/m^2) of the stimulus was constant throughout its presentation

and was the same across every band in the oriented grating.

1034

Block Design

Baseline, Ignore and Attend tasks were presented in a block design as shown in

Fig. 1D. Each run started with a Baseline block which lasted for 10 s and was presented

in every alternate block thereafter. Ignore and Attend blocks lasted for 20 s and were

presented randomly between Baseline blocks. The number of Ignore and Attend blocks

were balanced in a given run. Each run lasted 480s.

1041

Electrophysiology

Locations for muscimol injections in the SC and FEF were identified by single-

unit recording and electrical microstimulation. Single-unit activity was recorded using

tungsten in glass-coated electrodes with impedances of 1-2 MOhm (Alpha Omega Co.,

Inc., Alpharetta, GA). Electrode position was controlled with a Narishige microdrive. The

electrical signal was amplified and recorded online using the OmniPlex system (Plexon

Inc., Dallas, Texas). Response fields and saccade-related movement fields were

mapped by having the monkey perform the visually guided saccade task; we confirmed

saccade-related activity consistent with the known activity patterns in the FEF or SC.

Electrical microstimulation was also applied (70 ms train duration, 350 Hz, biphasic

pulses with duration of 0.25 ms) to evoke saccades with currents (40 μA in FEF; 20 μA

in SC) confirming that we were in the FEF or intermediate layers in SC (Bruce and

Goldberg, 1985; Robinson, 1972). All candidate sites were first identified by neuronal

recordings and electrical stimulation prior to the muscimol inactivation experiment; in

some cases, the FEF or SC site was verified immediately prior to muscimol injection

using the electrode placed within the injection cannula (Lovejoy and Krauzlis, 2010).

1058

Muscimol infusion

Reversible inactivation of the intermediate layers of the SC (n = 27; monkey #1:

19, monkey #2: 8) and FEF (n = 7; monkey #2) were done by injecting muscimol (5

mg/ml). The amount of muscimol injected ranged from 0.3 – 0.5 μl in SC and 1 – 2 μl in

FEF. Infusion was done using a custom-made apparatus modified from (Chen et al.,

2001), with an injection pump at a rate of 0.5 μl in 10 mins. For saline controls in SC,

0.3 – 0.5 μl of saline was injected at the same location in the intermediate layers of the

SC.

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Visually guided saccade task and mapping of affected visual field

In the saccade task, each trial started with the monkeys fixating a small square

stimulus (0.23° wide, 50 cd/m^2) placed at the center of the visual display. After 500 ms

of fixation, a second target (0.23° wide, 50 cd/m^2) was presented at some other location

in the visual display. Monkeys were required to maintain fixation until the central fixation

stimulus was turned off, 1-2 seconds after the onset of the peripheral target. At that

point, the monkeys should make a saccade to the second, peripheral target and fixate it

for at least 500 ms in order to receive a reward. The eye position data were used to

detect saccades and quantify saccade metrics offline using methods described

previously (Madelain et al., 2005).

Before imaging, monkeys performed the saccade task outside the scanner and

the location of the second target was systematically varied every trial in order to quantify

the metrics of saccades to targets across the visual field. We quantified the impairments

in saccade metrics during SC or FEF inactivation by measuring the difference in the

peak velocity for saccades made to targets at different locations in the visual field before

and during inactivation. The target locations where the peak velocities of the saccades

were impaired identified the affected visual field (Fig. 1E, 6B). Data were collected

beginning 30 minutes after the end of the muscimol infusion.

Inside the scanner, monkeys performed the saccade task every 8 minutes and

the location of the second target was alternated each trial between contralateral and

ipsilateral stimulus locations (radius: 8°; azimuth: 10°). The time course of muscimol

effect was measured as a difference in the saccade latency to targets in the

contralateral affected visual field compared to targets in the ipsilateral unaffected visual

field (Fig. 1E). We measured the impairment on the saccade latency instead of peak

velocity in the scanner because, the low sampling frequency of the eye tracker in the

scanner limited the accurate measurement of peak velocities.

1094

fMRI data collection

Anatomical and functional images were collected in a vertical magnet (4.7T, 60

cm vertical bore; Bruker Biospec) equipped with a Bruker S380 gradient coil. EPI

volumes were acquired using a custom built transmit and 4-channel receive RF coil

system (Rapid MR International). In each run, we collected 192 whole-brain EPI

volumes at an isotropic voxel resolution of 1.5 mm and at a TR of 2.5 s.

1101

fMRI Analysis

Preprocessing of the fMRI data was done using AFNI/SUMA software package

(Cox, 1996). Raw images were converted to AFNI data format. EPI volumes in each run

were slice-time corrected using *3dTshift*, followed by correction for static magnetic field

inhomogeneities using the *PLACE* algorithm (Xiang and Ye, 2007). All EPI volumes

were motion-corrected using *3dvolreg* and were registered to the session anatomical

using *3dAllineate*. To combine EPI data across multiple sessions for a given animal, all

sessions for a given animal were registered to a template session. A high resolution

anatomical of each monkey was registered to the corresponding template session

anatomical to overlay functional results in monkey's native space. To overlay D99 atlas

boundaries on the functional results, D99 anatomical in AFNI was registered to each

monkey's native space (Reveley et al., 2017). Surface maps were generated for D99

anatomical in each monkey's native space using CARET from a white matter

segmentation mask (Van Essen et al., 2001). Surface maps of D99 in each monkey's

native space were viewed in SUMA overlaid with anatomical boundaries and functional

results.

1118

Functional maps of attention-related modulation

To identify voxels that were modulated by attention we performed a GLM

analysis using *3dDeconvolve* in AFNI. Attend and Ignore conditions were included as

regressors of interest and Baseline condition, motion correction parameters were

included as regressors of no interest (baseline model). To control for the effects caused

by any differences during Attend and Ignore blocks in blinks (Wilcoxon rank sum test, p

= 0.007 (Monkey # 1), p = 0.99 (Monkey # 2)), saccadic eye movements within the

fixation window (Wilcoxon rank sum test, p < 0.0001 (Monkey # 1), p < 0.0001 (Monkey

2)), rewards (Wilcoxon rank sum test, p < 0.0001 (Monkey # 1), p < 0.0001 (Monkey

2)) and joystick movements (Wilcoxon rank sum test, p = 0.79 (Monkey # 1), p = 0.53

(Monkey # 2)), we included these factors as part of the regression model. Reward

times, joystick event times (press and release), blink times and saccade times (left and

right) were convolved with the hemodynamic impulse response function and were

included as part of the baseline model. In the blocks of all three conditions for both

monkeys, the median duration of fixation was above 85% of the block duration.

Saccades within the fixation window (magnitude less than 1°) were detected using

previously described methods (Madelain et al., 2005). T-scores contrasting Attend and

Ignore conditions were projected on to the inflated maps to show voxels modulated by

attention. All functional maps were thresholded (t-score > 5.02) to correct for multiple

comparisons (p<0.05, Bonferroni correction).

1139

Functional regions of interest and attention-related modulation

Functional regions of interest (ROIs) were identified based on the local maxima

of the attention-related modulation map from the control sessions for each hemisphere

using *3dExtrema* in AFNI. The BOLD time-course for each Attend or Ignore block was

computed as a % change in BOLD relative to the BOLD in Baseline block preceding it.

For each ROI, an average time-course was constructed by pooling time-courses of all

voxels within a 2mm radius around the local maxima across all blocks from all sessions.

D-prime was computed for each ROI as a measure of attention-related modulation from

the Attend and Ignore distributions of BOLD values taken from the TRs 2 – 8 of each

block. Attend and Ignore distributions were constructed by pooling BOLD values across

voxels in a given ROI and across blocks from different sessions. The mean and

variance of the Attend (μ_A, σ_A^2) and Ignore (μ_I, σ_I^2) distributions were used to compute d-

prime (d') following equation 1. The source of the variance in the Attend and Ignore

distributions came from pooling BOLD values across blocks, sessions and voxels in a

given ROI.

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1156 $d' = (\mu_A - \mu_I)/(\sqrt{1/2(\sigma_A^2 + \sigma_I^2)})$ Equation 1

1157

Voxel-wise ANOVA

For each voxel, we performed ANOVA with two factors and two levels each –

covert attention (Attend and Ignore conditions) and neglect (control and inactivation).

The 2x2 factorial design for each voxel was based on the BOLD values taken from the

TRs 2 – 8 of Attend and Ignore time courses extracted from the control and neglect

sessions. F-statistic of the interaction term was projected onto the inflated maps to show

the effect of inactivation on attention-related modulation. For every voxel, the sign of the

difference in attention-related modulation between neglect and control

$(d'_{Neglect} - d'_{Control})$ was added to the F-statistic of the interaction term to differentiate

the decrease in modulation from increase in modulation.

1168

Stimulus mapping experiment

To identify voxels responding to foveal and peripheral stimuli locations, a

flickering checker board stimulus (4 Hz) that had concentric rings of 2º width spanning

up to 12º eccentricity was used. In foveal visual stimulation blocks, the checker board

stimulus was masked everywhere except for the central 2º radius. In peripheral visual

stimulation blocks, the checker board stimulus was masked everywhere except for the

two eccentric stimulus locations used in the attention tasks. The foveal and peripheral

stimulation blocks (20 s duration) were interleaved with fixation blocks (10 s duration). A

total of 258 runs (150 in Monkey #1; 108 in Monkey # 2) were collected in both monkeys

across 13 sessions. Functional maps showing peripheral and foveal voxels were

created using the same methods as described for creating functional maps for the

attention tasks.

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Figure 1

Figure 2

A Control
B Neglect
Monkey # 1

8Bs PGa MST PEa LIPv
8Ad LIPd
46d V3d
V2
46v V1
8Av V4
45b MT
TPO IPa TEO FST

t-scores
Attend Vs Ignore

C Control
D Neglect
Monkey # 2

LIPv PEa MST PGa 8Bs 8Ad
LIPd 46d
V3d 46v
V2 8Av
V4 45b
MT
FST TEO IPa TPO

Figure 3

Figure 4

Figure 5

A Ignore task

Fixate (1 - 3 s)   Detect dim (0.8 s)

B Attend task

Fixate (1 - 3 s)   Detect pulse (0.8 s)

C Attention deficits

% Hit rate Contralateral pulse

% Hit rate Ipsilateral pulse

○ Control
○ Neglect

D Control

E Neglect

t-score
Attend Vs Ignore

F Effect in aFST/IPa

PGa

IPa   FST

F-statistic

G Location: AP +5.75 mm

Figure 6

A FEF localisation

B Visual field map

C Control

D Neglect

t-score
Attend Vs Ignore

E Effect in aFST/IPa

MT

FST

PGa

IPa

F-statistic

F Location: AP +7 mm