Eyes on me: an fMRI study of the effects of social gaze on action control

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Previous evidence suggests that 'social gaze' can not only cause shifts in attention, but also can change the perception of objects located in the direction of gaze and how these objects will be manipulated by an observer. These findings implicate differences in the neural networks sub-serving action control driven by social cues as compared with nonsocial cues. Here, we sought to explore this hypothesis by using functional magnetic resonance imaging and a stimulus–response compatibility paradigm in which participants were asked to generate spatially congruent or incongruent motor responses to both social and nonsocial stimuli. Data analysis revealed recruitment of a dorsal frontoparietal network and the locus coeruleus for the generation of incongruent motor responses, areas previously implicated in controlling attention. As a correlate for the effect of 'social gaze' on action control, an interaction effect was observed for incongruent responses to social stimuli in sub-cortical structures, anterior cingulate and inferior frontal cortex. Our results, therefore, suggest that performing actions in a—albeit minimal—social context significantly changes the neural underpinnings of action control and recruits brain regions previously implicated in action monitoring, the reorienting of attention and social cognition.

INTRODUCTION

Human communication relies heavily on nonverbal cues. For example, the interpersonal coordination of gaze, i.e. 'social gaze', is known to have an important regulatory function in social interactions as such gaze shifts result in a change of our perception and evaluation of an interactor (Argyle and Cook, 1976; Macrae *et al.*, 2002; Bayliss and Tipper, 2006; Kuzmanovic *et al.*, 2009). Gaze shifts can, however, also direct our attention automatically and rapidly toward an aspect of the environment (Friesen and Kingston, 1998; Ricciardelli *et al.*, 2002; Bayliss *et al.*, 2006; Frischen *et al.*, 2007). Notably, the underlying mechanisms appear to be different from those of nonsocial, exogenous cues directing our attention as previous evidence suggests that attentional orienting driven by social cues involves a different neural network from orienting driven by nonsocial cues (Kingstone *et al.*, 2004; Hietanen *et al.*, 2006; Tipper *et al.*, 2008; Greene *et al.*, 2009). In addition to effects on attentional reorienting, the perception of gaze shifts has been shown to affect the perception of objects located in the direction of gaze and to influence how a human observer will

manipulate and handle such objects, which is suggestive of an interaction between mechanisms of gaze perception and action control (Becchio *et al.*, 2007, 2008). In this study, we sought to investigate the possibility that the perception of gaze shifts of another person—as compared with nonsocial cues—might influence the performance and neurophysiology of a simple motor act.

For this purpose, we modified a stimulus–response compatibility (SRC) paradigm in a way that it included a social stimulus. Participants were asked to generate a motor response, i.e. a button press performed with either left or right index finger, which was either spatially congruent or incongruent (response type: CON *vs* INC), in response to a change in a centrally presented visual stimulus occurring either toward the left or right. As visual stimuli, the face of an anthropomorphic virtual character performing gaze shifts and a square exhibiting a displacement to the left or right before a face-like background were used (stimulus type: SOC *vs* OBJ; see Figure 1). In order to generate a gaze-mediated social context, the face was shown with direct gaze toward the participant whenever no gaze shifts occurred to prompt motor responses as 'eye contact' is known to be a powerful communicative cue signaling interest and often precedes inter-individual interaction (Schilbach *et al.*, 2006; George and Conty, 2008; Senju and Johnson, 2009). Taken together, our study made use of a 2×2 factorial design, in which participants were engaged while undergoing functional magnetic resonance imaging (fMRI) at 3 T.
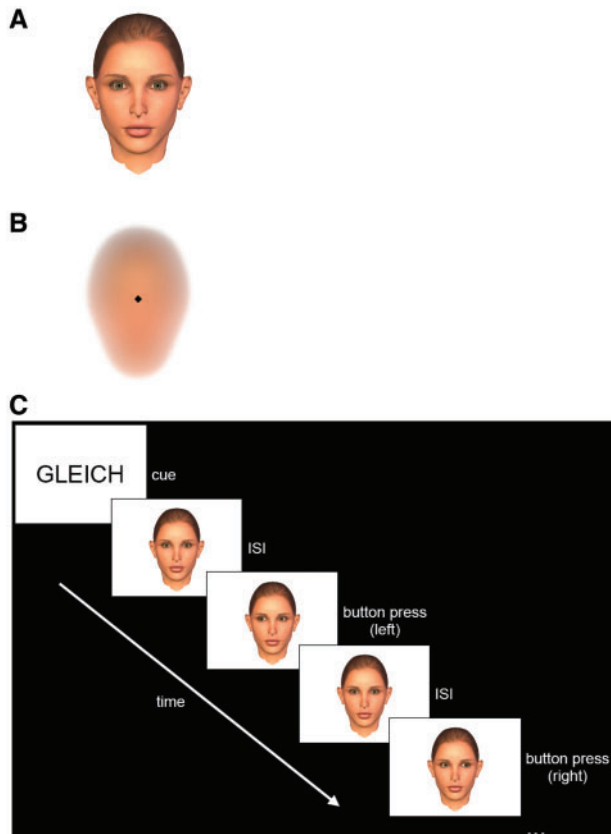
We hypothesized that participants' performance in the SRC task would be modulated by the stimulus type, with

Fig. 1 Social (**A**) and nonsocial stimuli (**B**) used in the study. (**C**) Exemplary depiction of event structure. ISI: inter-stimulus interval.

the gaze-mediated social context leading to an enhancement of action control reflected by a decrease in reaction time. With respect to the underlying neural substrates, we expected recruitment of distinct neural networks depending upon the stimulus type; while the perception of the face stimulus—regardless of response type—was expected to result in activation of inferotemporal cortex (Kanwisher et al., 1997), the perception of a moving, nonsocial stimulus was expected to rely on higher order visual cortex (Sarkheil et al., 2008) as well as posterior parietal cortex (Kawasaki et al., 2008). Furthermore, we expected to replicate previous findings that demonstrated the recruitment of a frontoparietal 'dorsal attention network' (DAN) including the intra-parietal sulci (IPS), right temporoparietal junction (TPJ), premotor cortex (PMC) and right dorsolateral prefrontal cortex (DLPFC) to underlie the generation of incongruent motor responses regardless of stimulus type (Corbetta et al., 2008).

Lastly and most specific to our key research question, we hypothesized to observe an interaction effect at the neural level in brain areas whose involvement for the generation of incongruent responses was expected to depend upon stimulus type. Here, we expected that generating an incongruent motor response in a gaze-mediated social context would differentially engage brain regions known to show an interaction between cognitive and motivational aspects of response inhibition, such as the inferior frontal gyrus (Padmala and Pessoa, 2009) and the basal ganglia (Forstmann et al., 2008). Such areas have also been described as belonging to a 'ventral attention network' (VAN) that allows a reorienting response, which changes the current course of action in order to respond to advantageous or threatening, i.e. behaviorally relevant stimuli (Corbetta et al., 2008).

METHODS

Participants

Twenty-three right-handed healthy volunteers (aged 21–37 years, mean age: 27.06; 12 females) with no record of neurologic or psychiatric illness participated in this fMRI study. All volunteers were naive with respect to the experimental task as well as to the purpose of the study. Handedness was confirmed using the Edinburgh Handedness Questionnaire (Oldfield, 1971). All subjects gave informed written consent to the study protocol that had been approved by the local ethics committee of the Medical Faculty of the University of Cologne, Germany.

Experimental protocol

Before participation, all participants received standardized instructions and were familiarized with the task. Participants were instructed to respond as fast and correct as possible to each change of the target stimulus by pressing a button on an MRI-compatible response pad (LumiTouch, Burnaby, Canada) according to the task condition. The change in target stimulus could either be (i) a gaze shift toward the right or left shown by an anthropomorphic virtual character which otherwise looked straight ahead (SOC; see Figure 1A and C) or (ii) the displacement of a square of the same size as the pupil of the face toward the left or right from a central starting position (OBJ; see Figure 1B). The offset in pixel coordinates as well as the timing was equivalent in both social and nonsocial displays. For the congruent condition (CON), subjects were instructed to respond with the ipsilateral hand (i.e. pressing with their left index finger to a left-moving stimulus and with their right index finger to a right-moving stimulus). For the incongruent condition (INC), subjects were instructed to respond with the contralateral hand (i.e. pressing with their left index finger to a right-moving stimulus and with their right index finger to a left-moving stimulus). Our study, therefore, made use of a 2×2 factorial design. Participants neither did receive training prior to performing the task inside the scanner nor did they receive feedback at any point during the experiment.

Visual stimuli were presented using the software package Presentation (Version 11.3) and were displayed on a custom-built, shielded TFT screen at the rear end of the scanner visible via a mirror mounted on the headcoil ($\sim 12° \times 8°$ viewing angle, 245 mm distance from the subject's eyes). During the experiment, task blocks lasting

57–63 s were periodically alternated with rest periods ('baseline') that lasted 15–17 s (uniformly jittered). Each task block started with an instruction cue, i.e. the German word 'GLEICH' (i.e. 'SAME') for the CON or the German word 'GEGEN' (i.e. 'OPPOSITE') for the INC, being presented for 1500 ms to inform the subject, which of the two experimental conditions had to be performed throughout the subsequent block in that either the social or the nonsocial stimulus would be presented (Figure 1). Regardless of the condition, 10, 12 or 14 events per block (50% left- and 50% right-moving stimuli presented at random) occurred. The inter-stimulus interval (ISI) was jittered between 2 and 6 s. In the course of the entire experiment, each of the two conditions (congruent, incongruent) was presented in 12 individual blocks. The order of these 24 blocks was pseudo-randomized and counterbalanced across subjects.

Behavioral data analysis

The dependent variables were the reaction time (RT) of the responses given and the percentage of correct responses (CR). The behavioral measurements obtained during the fMRI experiment were analyzed off-line using MATLAB (MathWorks, Natick, MA, USA). RTs <150 ms or >1600 ms were regarded as anticipation errors or missed responses, respectively, and discarded from the later analysis. Here, it is important to note that using a centrally presented stimulus allows us to exert control over participants' eye movements. In order to perform the task and generate reactions to the changes in the visual stimulus, participants had to maintain fixation to the center of the screen throughout the experiment. Otherwise they would miss or react more slowly to the visual change. Using RTs as an a priori filter for the selection of events, therefore, allows us to analyze those events that are least likely to differ with respect to eye movements performed by participants across conditions. The effect of the experimental factors (response type: congruent vs incongruent; stimulus type: social vs nonsocial) on mean RT and the CR percentage was compared by means of a repeated measures analysis of variance (repeated measures ANOVA).

fMRI

Images were acquired on a Siemens Trio 3T whole-body scanner (Erlangen, Germany) using blood oxygen level-dependent (BOLD) contrast (Gradient-echo EPI pulse sequence, TR = 2200 ms, in plane resolution = 3.1 × 3.1 mm, 36 axial slices, 3.1 mm thickness) covering the whole brain. Image acquisition was preceded by four dummy images allowing for magnetic field saturation. These were discarded prior to further processing. Images were analyzed using SPM5 (www.fil.ion.ucl.ac.uk/spm). First, the EPI images were corrected for head movements by affine registration using a two-pass procedure, by which images were initially realigned to the first image and subsequently to the mean of the realigned images. After realignment, the mean EPI image for each subject was spatially normalized to the MNI single subject template using the 'unified segmentation' approach (Ashburner and Friston, 2003). The resulting parameters of a discrete cosine transform, which define the deformation field necessary to move the subjects' data into the space of the MNI tissue probability maps, were then combined with the deformation field transforming between the latter and the MNI single subject template. The ensuing deformation was subsequently applied to the individual EPI volumes that were hereby transformed into the MNI single subject space and resampled at $2 \times 2 \times 2$ mm^3 voxel size. The normalized images were spatially smoothed using an 8 mm FWHM Gaussian kernel to meet the statistical requirements of a general linear model (GLM) and to compensate for residual macroanatomical variations across subjects.

The fMRI data were analyzed using a GLM as implemented in SPM5. Each experimental condition was modeled using a series of stick functions denoting the individual events for which a correct response had been generated. These were convolved with a canonical hemodynamic response function (HRF) and its first-order temporal derivative. Low-frequency signal drifts were filtered using a cutoff period of 128 s. Parameter estimates were subsequently calculated for each voxel using weighted least squares to provide maximum likelihood estimators based on the temporal autocorrelation of the data (Kiebel and Holmes, 2003). No global scaling was applied. For each subject, simple main effects for each experimental condition were computed by applying appropriate baseline contrasts. These individual first-level contrasts were then fed into a second-level group analysis using an ANOVA (factor: condition, blocking factor: subject) employing a random-effects model. In the modeling of variance components, we allowed for violations of sphericity by modeling nonindependence across images from the same subject and allowing unequal variances between conditions and subjects using the standard implementation in SPM5.

On the second level, the main effect of social stimuli (SOC) [(CON_SOC + INC_SOC) > (CON_OBJ + INC_OBJ)] as well as the main effect of nonsocial stimuli (OBJ) were calculated [(CON_OBJ + INC_OBJ) > (CON_SOC + INC_SOC)]. Furthermore, we analyzed the main effect of congruent response (CON) [(CON_SOC + CON_OBJ) > (INC_SOC + INC_OBJ)] as well as the main effect of incongruent response (INC) [(INC_SOC + INC_OBJ) > (CON_SOC + CON_OBJ)]. To test for statistical interactions between the main effects, i.e. relative activation for INC × SOC [(INC_SOC – CON_SOC) > (CON_OBJ – INC_OBJ)] and relative activation for INC × OBJ [(INC_OBJ – CON_OBJ) > (CON_SOC – INC_SOC)] appropriate contrasts were calculated. The resulting SPM(T) maps were interpreted by referring to the probabilistic behavior of Gaussian random fields (Worsley et al., 1996) and thresholded at $P < 0.05$ (cluster-level corrected for multiple

comparisons). The cluster-forming threshold was set to $P_{uc} < 0.001$.

Functional activations were anatomically localized by using the SPM anatomy toolbox (Eickhoff *et al.*, 2007) employing a maximum probability map (MPM). This map (Eickhoff *et al.*, 2006) denotes the most likely anatomical area at each voxel of the MNI single subject template based on probabilistic cytoarchitectonic maps derived from the analysis of cortical areas in a sample of 10 human post-mortem brains, which were subsequently normalized to the MNI reference space. If no cytoarchitectonic maps were available, the macro-anatomical labels are provided based on the automated anatomic labeling (AAL) atlas (Tzourio-Mazoyer *et al.*, 2002).

Combining reaction time and fMRI data

To assess correlations between BOLD signal change and an increase of RT for incongruent responses to social and nonsocial stimuli, appropriate first level contrasts (INC_SOC > CON_SOC and INC_OBJ > CON_OBJ, as well as the inverse) were used in a one-sample *t*-test as implemented in SPM5 on the second level while using the individual RT differences as a covariate.

RESULTS

Behavioral data

Mean RTs and percentages of correct responses measured during scanning are shown in Figure 2. Repeated measures ANOVA of RT showed a significant main effect of response type [congruent *vs* incongruent; $F(1,31) = 30.67$, $P < 0.001$] and of stimulus type [social *vs* nonsocial; $F(1,31) = 74.32$, $P < 0.001$]. Percentages of correct responses also showed a significant main effect of response type [congruent *vs* incongruent; $F(1,31) = 31.44$, $P < 0.001$] and of stimulus type [social *vs* nonsocial; $F(1,31) = 54.38$, $P < 0.001$]. No significant interaction was observed.

Neural correlates

Neural correlates of all main effects and their interactions are summarized in Table 1. Figure 3 shows the SPMs of suprathreshold clusters of the main effects and their interaction as overlay images onto the T1-weighted template as provided in SPM5 and includes plots of the contrast estimates for the principally activated voxels within clusters of interest across all experimental conditions.

Incongruent responses regardless of the stimulus type, i.e. the main effect of incongruent response (INC) [(INC_SOC + INC_OBJ) > (CON_SOC + CON_OBJ)], were associated with increased neural activity in a frontoparietal network comprising the inferior parietal lobe, right middle frontal gyrus, left anterior and right middle cingulate cortex, left inferior frontal gyrus, right precentral gyrus and the precuneus. Additionally, differential increases of neural activity in the locus coeruleus bilaterally and the cerebellar vermis were noted. Conversely, the main effect of congruent
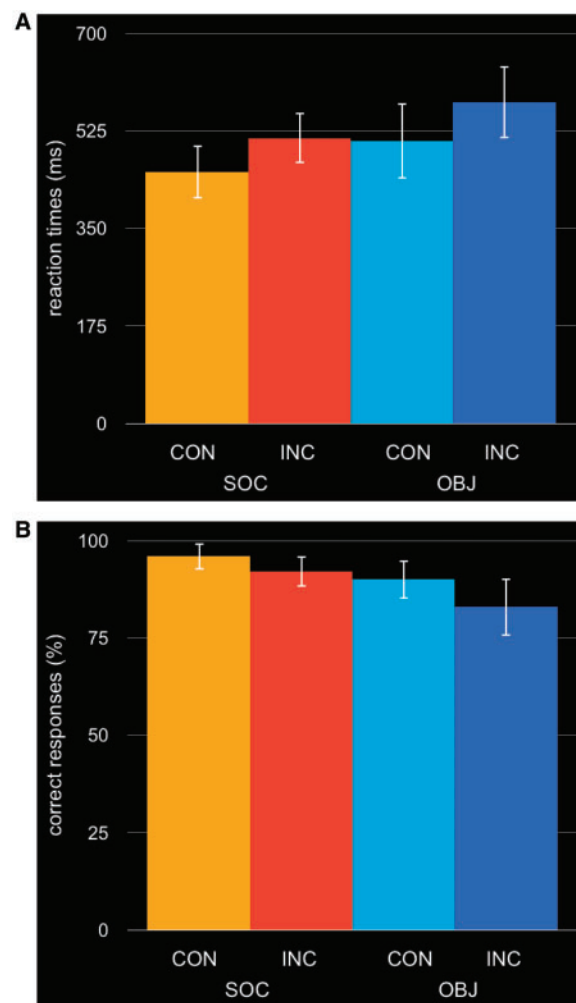
Fig. 2 Mean reaction times (**A**) and percentages of correct responses (**B**) across all experimental conditions. Error bars depict standard deviation.

response (CON) did not show any suprathreshold voxels of activation.

Additionally, main effects dependent upon stimulus type were detected; while the main effect of nonsocial stimuli (OBJ): [(CON_OBJ + INC_OBJ) > (CON_SOC + INC_SOC)] demonstrated recruitment of occipital and temporoparietal cortices, the main effect of social stimuli (SOC) [(CON_SOC + INC_SOC) > (CON_OBJ + INC_OBJ)] revealed involvement of inferotemporal gyrus, the medial temporal lobes extending into the right amygdala, the left inferior frontal gyrus, ventral and dorsal medial prefrontal cortex, left and right paracentral lobule, left inferior temporal gyrus and the right temporal pole.

To test for statistical interactions between the main effects, i.e. relative activation for INC × SOC [(INC_SOC − CON_SOC) > (CON_OBJ − INC_OBJ)] and relative activation for INC × OBJ [(INC_OBJ–CON_OBJ) > (CON_SOC − INC_SOC)], appropriate contrasts were calculated. A statistical interaction between the main effects for INC × SOC was noted in the dorsal striatum, left anterior cingulate cortex,

Table 1 Neural correlates

Brain region	x	y	z	k	T
Common activations of congruent response (CON > INC)					
No suprathreshold voxels					
Common activations of incongruent response (INC > CON)					
Left inferior parietal lobule	−39	−35	39	6723	5.85[#]
Right middle frontal gyrus	33	45	26	1112	4.43
Right inferior parietal lobule	44	−47	41	854	4.47
Right middle frontal gyrus	30	−2	56	844	6.11[#]
Left anterior cingulate cortex	6	8	30	681	4.79
Right middle cingulate cortex	2	−24	42	619	4.78
Left inferior frontal gyrus	−32	30	−3	498	6.13[#]
Right thalamus	29	−5	9	455	4.61
Left locus coeruleus	−8	−28	−18	374	4.95
Cerebellar vermis	6	−57	−18	369	4.14
Right precentral gyrus	27	−12	71	364	4.40
Right precuneus	17	−44	38	204	4.14
Right locus coeruleus	9	−27	−18	169	4.52
Common activations of nonsocial stimuli (OBJ > SOC)					
Right superior occipital gyrus	29	−83	26	2991	5.57[#]
Left middle occipital gyrus	−47	−68	0	1091	6.19[#]
Left cuneus	−9	−77	29	1017	4.40
Left inferior parietal sulcus	−38	−42	39	422	5.39[#]
Common activations of social stimuli (SOC > OBJ)					
Lingual gyrus	17	−98	−9	14 335	16.91[#]
Right hippocampus	24	−27	−5	1938	9.65[#]
Left hippocampus	−24	−29	−8	1299	8.09[#]
Left inferior frontal gyrus	−44	−18	20	325	4.67
Left dorsal medial prefrontal cortex	−5	57	26	276	4.16
Left paracentral lobule	−11	−30	54	268	4.18
Left inferior temporal gyrus	−60	−44	−17	256	4.79
Left ventral medial prefrontal cortex	−3	53	−21	239	4.26
Right temporal pole	53	11	−17	189	4.46
Right paracentral lobule	5	−29	66	166	3.88
Common activations of statistical interaction INC × SOC					
Left dorsal striatum	−17	2	8	787	4.75
Left inferior frontal gyrus	−51	14	8	550	6.18[#]
Left anterior cingulate cortex	−8	30	21	296	4.55
Left thalamus	−6	−14	8	150	3.91
Right superior frontal gyrus	14	62	21	141	4.02
Common activations of statistical interaction INC × OBJ					
No suprathreshold voxels.					

Main effects and statistical interaction at $P < 0.05$ cluster-level corr. for multiple comparisons; MNI coordinates of principally activated voxels for each cluster are given. [#]Also significant at $P < 0.05$ FWE voxel-level corr.

the left (mediodorsal) thalamus and left inferior frontal gyrus. No suprathreshold activation was observed for the inverse contrast of INC × OBJ. To ensure that the observed interaction effect is not driven by the second comparandum, i.e. due to a negative contrast in the nonsocial condition, we also analyzed the relevant simple contrast (INC_SOC > CON_SOC) which was inclusively masked by the respective interaction at $P < 0.0001$ uncorr. and then thresholded at the cluster-level corrected threshold. This analysis corroborated the above-described findings for the interaction effect INC × SOC.

In order to investigate possible overlap in activations between the interaction effect observed for INC × SOC and the main effect of incongruent response, a conjunction analysis (conjunction null hypothesis, thresholded at 0.05 FWE corr.) was performed: [(INC_SOC > CON_SOC) > (CON_OBJ > INC_OBJ)] ∩ [(INC_SOC + INC_OBJ) > (CON_SOC + CON_OBJ)]. This analysis did not show any suprathreshold voxels of activation that suggests the existence of distinct patterns of activations for the respective contrasts. In order to ensure that the interaction effect revealing a specific congruency effect in the social condition (INC × SOC) is not due to a negative contrast (deactivation) in the nonsocial condition, an inclusive masking procedure was applied for INC × SOC and the simple contrast SOC_INC > SOC_CON. This analysis corroborated the above-described findings of an interaction effect in the dorsal striatum, anterior cingulate cortex, the mediodorsal thalamus and inferior frontal gyrus.

### Combining reaction time and fMRI data

To investigate brain behavior correlations with respect to the increase of RT for incongruent responses to social and nonsocial stimuli, the RT incongruency costs were used as a covariate in a second-level analysis of first-level contrasts of activation differences for incongruent as compared with congruent responses for social and nonsocial stimuli, respectively. When using the covariate to assess correlations of RT incongruency costs for social stimuli with the activation differences for incongruent responses to social stimuli (INC_SOC > CON_SOC), this analysis revealed a differential increase of neural activity in the ventral striatum (see Figure 4; MNI: 8, −1, −8; k: 159 voxels, T: 6.17). Importantly, the procedure failed to show any suprathreshold activations when using the covariate in conjunction with the contrast targeting activation differences for congruent responses to social stimuli (CON_SOC > INC_SOC). Consequently, the results of our correlation analysis can be assumed to be specifically related to RT incongruency costs for social stimuli. Also, we did not observe suprathreshold activations when using the RT difference for the nonsocial stimuli in the same way to analyze the relevant contrasts (INC_OBJ > CON_OBJ and CON_OBJ > INC_OBJ).

DISCUSSION

We used fMRI to investigate the impact of a gaze-mediated social context on the neural bases of the performance of manual actions as assessed by an SRC task. The data suggest that the perception of nonsocial stimuli leads to activation of extrastriate visual and posterior parietal cortices, while the perception of social stimuli results in activation of inferotemporal cortex, the amygdala and medial prefrontal cortex. Results also demonstrate recruitment of a frontoparietal network and the locus coeruleus for the generation of incongruent motor responses regardless of the stimulus type. Furthermore, results demonstrate an interaction between the main effects for incongruent responses to social stimuli in sub-cortical structures (dorsal striatum, mediodorsal thalamus), anterior cingulate and inferior frontal cortex that is
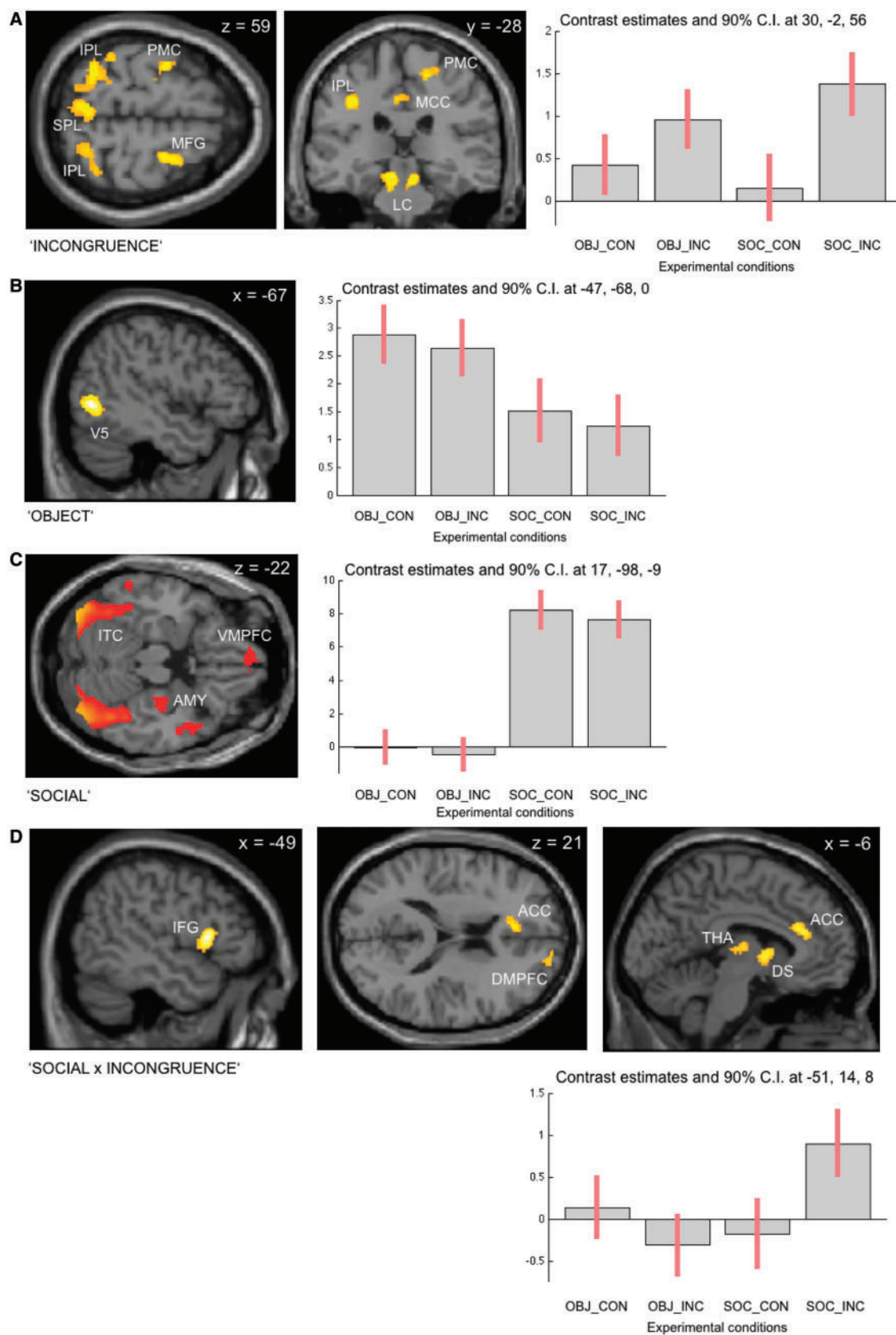
Fig. 3 Neural correlates (**A**–**C**: main effects; **D**: statistical interaction; all shown at $P < 0.05$ cluster-level corr. for multiple comparisons. IPL: inferior parietal lobule, SPL: superior parietal lobule; PMC: premotor cortex, MCC: middle cingulate cortex, LC: locus coeruleus, V5: middle occipital gyrus, ITC: inferotemporal cortex, AMY: amygdala, VMPFC: ventral medial prefrontal cortex, ACC: anterior cingulate cortex, DMPFC: dorsal medial prefrontal cortex, THA: thalamus, DS: dorsal striatum).
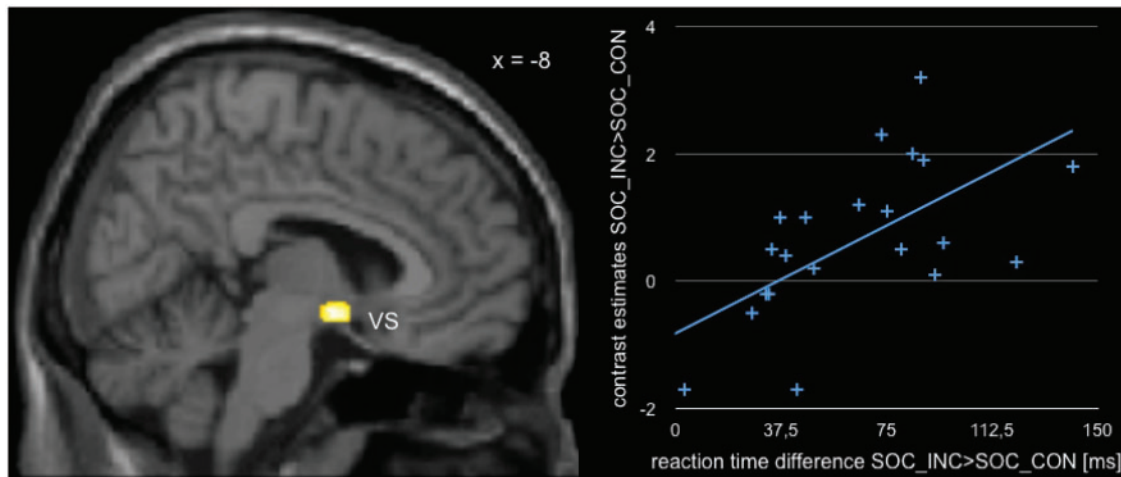
Fig. 4 Neural correlate of reaction time difference for incongruent as compared to congruent responses to social stimuli (VS: ventral striatum). Data plot shown for illustrative purposes only.

in line with the idea that social context influences the neuronal bases of action control.

Neural correlates of action control

The observed RT difference between congruent and incongruent responses—regardless of the stimulus type—is in accordance with the available literature. Most studies report an increase in RT of 40–80 ms (so-called incongruency cost) when subjects have to react in a spatially incongruent manner to a visual stimulus (Proctor and Reeve, 1990; Iacoboni *et al.*, 1996; Matsumoto *et al.*, 2004). This is highly consistent with the incongruency cost observed in our study both for social and nonsocial stimuli. These differences in RT are deemed to reflect the extra 'computational load' associated with the inhibition of the reflexive answer, processes of attentional reorienting and the generation of the appropriate yet incongruent motor response (Iacoboni *et al.*, 1996). Our analysis of the fMRI data revealed that these processes were associated with increased neural activity in the inferior, middle and superior frontal gyrus, inferior and superior parietal cortex bilaterally, the precentral gyrus and anterior cingulate cortex as demonstrated by the main effect of incongruent responses which is in line with the available literature (Iacoboni *et al.*, 1996; Nobre *et al.*, 2001; Corbetta and Shulman, 2002; Cisek and Kalaska, 2005). Activity in this DAN has been described as the neural correlate of attentional top-down control mechanisms, which are assumed to bias the processing of stimulus features in such a way that they allow a selection of them based on internal goals or expectations and a link to appropriate motor responses (Corbetta *et al.*, 2008). Consistently, lesion studies have implicated (predominantly right) posterior parietal cortex for the maintenance of attention to spatial locations over time as well as sensorimotor transformations relevant for movements (Malhotra *et al.*, 2009). Here, parallels between SRC and anti-saccade paradigms seem noteworthy as the

latter are also known to engage the frontal and supplementary eye fields during the performance of incongruent actions (Munoz and Everling, 2004; Pierrot-Deseilligny *et al.*, 2004). Moreover, these brain regions overlap largely with frontal and parietal lobe activations observed in similarly structured tasks that require the use of a different motor effector (e.g. anti-pointing tasks; Connolly *et al.*, 2000).

Furthermore, our results demonstrate recruitment of the cerebellum and sub-cortical areas such as the thalamus and the brain stem for the generation of incongruent responses regardless of stimulus type. Intriguingly, the observed activations in the brain stem localize precisely to the locus coeruleus (LC) bilaterally, the key noradrenergic brain site (Minzenberg *et al.*, 2008; Keren *et al.*, 2009) and one of the most important neuromodulatory structures in light of its ascending projections to a multitude of brain regions (Sara, 2009). Consistently, LC activity enhances arousal via actions within multiple sub-cortical regions and influences cognitive functions by facilitating the functional integration of brain regions (Coull, 1999; Berridge, 2008), among them cortex-based attentional processes (Corbetta *et al.*, 2008). The latter appears to be in line with our results, which replicate the recruitment of a frontoparietal DAN and co-activation of the LC to underlie the generation of spatially incongruent motor responses regardless of stimulus type (Corbetta *et al.*, 2008).

Neural correlates of face processing

Furthermore, our fMRI analysis demonstrates significant differences in neural processing related to stimulus type, regardless of the kind of motor response given. The perception of the social stimuli, i.e. a face performing gaze shifts, as compared to the nonsocial stimuli, i.e. a moving black square, results in recruitment of inferotemporal cortex, a brain area known to be involved in face processing (Kanwisher *et al.*, 1997). Also, the data demonstrate

involvement of the medial temporal lobe (bilateral hippo-campus) and the right amygdala. While the former might be related to mnemonic processes in response to seeing a face, the latter has been implicated as a 'relevance detector' whose activation may plausibly result in an enhancement of stimulus processing and could thereby contribute to the decrease in reaction times for social stimuli (Wright and Liu, 2006; Ewbank *et al.*, 2009; N'Diaye *et al.*, 2009; Zaretsky *et al.*, 2009). Additionally, a differential increase of neural activity for social stimuli was observed in both the ventral and dorsal portions of medial prefrontal cortex. While the former has been related to mentalizing, i.e. the processing of mental states of other agents, the latter has been interpreted in terms of evaluative processes with respect to the observed stimulus (Schilbach *et al.*, 2006, 2010).

Neural correlates of action control in a social context

With this study, we specifically investigated the hypothesis that introducing gaze cues into an established SRC paradigm would allow us to investigate the impact of a gaze-mediated social context on the neural correlates of action control. Here, we expected that generating an incongruent motor response to a social rather than a nonsocial stimulus would alter the above-described neural network sub-serving action control to include brain areas which have been implicated in attentional reorienting, response inhibition and action understanding (Pobric and Hamilton, 2006; Corbetta *et al.*, 2008; Swick *et al.*, 2008). In line with this hypothesis, the fMRI data revealed an interaction of incongruent responses to social stimuli as evidenced by a differential increase of neural activity in the dorsal striatum, the mediodorsal thalamus, left inferior and right superior frontal gyrus and anterior cingulate cortex.

Numerous studies have demonstrated activations of inferior frontal cortex during the observation of actions and it has also been demonstrated that this brain region, indeed, seems to be necessary for making perceptual judgements about other people's actions thereby contributing to action understanding (Pobric and Hamilton, 2006). On the other hand, left inferior frontal gyrus has also been related to response inhibition and cognitive control (Derrfuss *et al.*, 2005; Sridharan *et al.*, 2008; Swick *et al.*, 2008; Christakou *et al.*, 2009; Goghari *et al.*, 2009; Jakobs *et al.*, 2009). More specifically, evidence suggests that the inferior frontal gyrus can be differentially engaged when cognitive and motivational signals interact during inhibitory control (Padmala and Pessoa, 2009; Schulz *et al.*, 2009). Similarly, inferior frontal cortex can be modulated by selective attention during action observation (Chong *et al.*, 2008). With respect to our paradigm, it makes sense to assume that the generation of an incongruent response to a face stimulus constitutes exactly such a situation. On the one hand, a face is likely to have a more pronounced impact on motivational processing while, on the other hand, gaze shifts in the context of manual actions might trigger imitative responses that require more

pronounced inhibitory effort (Ricciardelli *et al.*, 2002; Johnson-Frey *et al.*, 2003; Newman-Norlund *et al.*, 2010).

Apart from inferior frontal cortex, a differential increase of neural activity was also noted in the mediodorsal portion of the thalamus. This region is known to be anatomically connected to prefrontal cortices (Kito *et al.*, 2009) and has been suggested to be involved in the regulation of 'executive functions' (Minzenberg *et al.*, 2008), possibly affecting processes of action selection (Ostlund and Balleine, 2008). This has also been demonstrated for stimulus–response associations where medial frontothalamic circuits have been shown to underlie monitoring and reconfiguring of such associations (Parris *et al.*, 2007). Importantly, there is also evidence for anatomical and functional connectivity between the mediodorsal thalamus, basal ganglia and inferior frontal cortex—concomitantly activated in our study—suggested to constitute a 'cognitive control network' (Mitelman *et al.*, 2005; Aron *et al.*, 2007; Duann *et al.*, 2009). Consistently, left inferior frontal cortex has been shown to be specifically involved in response inhibition of automatic imitation by sending input to right premotor cortex (Bien *et al.*, 2009). We suggest that modulation of the latter processes might be particularly relevant in the case of social stimuli, which would account for a co-activation of inferior frontal gyrus, the mediodorsal thalamus and the dorsal striatum.

In parallel with the above-described findings, inferior frontal cortex has also been suggested to be part of the so-called VAN whose activity may contribute to attentional reorienting. In fact, this network has been shown to activate when behaviorally relevant targets are detected and has, therefore, been described to act as a 'circuit breaker' modulating top-down attentional processing in the DAN (Corbetta *et al.*, 2008). Consequently, activity in the VAN may serve as a 'switch' to internally directed cognition and could contribute to reorienting from one task state to another so that stimuli can be linked to behavioral responses (cf. Sridharan *et al.*, 2008). Based on our results, one might argue that social stimuli specifically engage the inferior frontal node of the VAN as a result of social stimuli imposing additional constraints on performing an incongruent reaction; gaze shifts can be assumed to not only affect spatial orienting, but are also known to be perceived as indicative of mental states and communicative intent (Kuzmanovic *et al.*, 2009; Schilbach *et al.*, 2010). Consistent with this suggestion, a statistical interaction was also observed in dorsal medial prefrontal cortex, a brain region that has been associated with the processing of mental states and communicative intentions (Amodio and Frith, 2006). Here, one could, therefore, tentatively suggest that the generation of an incongruent reaction to a face stimulus—inhibiting the urge to orient in the direction of the gaze shift—may not only lead to more pronounced inhibitory processes necessary to disengage from imitative reactions, but also to cognitive processes, which are related to processing the social stimulus in terms of its underlying intentionality. This finding might

also be taken to imply how deeply motor and intentional components of action are intertwined (Rizzolatti and Sinigaglia, 2007).

Finally, the dorsal striatum—which also demonstrates the interaction effect—has also been associated with action control, as the basal ganglia are known to provide a release mechanism for action generation (Casey *et al.*, 2002; Li *et al.*, 2008). Here, a relevant observation is that generating actions under time constraints has been shown to shift activations from more cortex-based processing toward the inclusion of the striatum, thereby facilitating faster responses as the striatum is known to release the motor system from global inhibition (Forstmann *et al.*, 2008). Similarly, the striatum is known to be involved in implicit motor learning (Karabanov *et al.*, 2010) and might thereby play an important role in segregating sensorimotor signals to multiple control processes (Mazzoni and Wexler, 2009), which might be relevant in the face of a more complex, social stimulus. Additionally, the striatum has been implicated in motivated behavior and reward-based processing (Blackwood *et al.*, 2003; Delgado *et al.*, 2003; Histed *et al.*, 2009; Morris *et al.*, 2010).

With respect to the generation of a social context by means of gaze cues, it is important to highlight that direct gaze or 'eye contact' before each event in the social condition must be assumed to be crucial to our experimental manipulation (Senju and Johnson, 2009). Future investigations using our paradigm could explore this systematically and assess whether and how the observed impact of the face stimulus on the neural correlates of action control is modulated by the face looking directly toward the human observer or not before producing a gaze shift (Conty *et al.*, 2010).

Neural correlate of reaction time increase for incongruent responses to social stimuli

To investigate brain behavior correlations with respect to the increase of RT for incongruent responses to social and non-social stimuli, the RT incongruency costs were used as a covariate in our analysis. This procedure, indeed, demonstrated a correlation between neural activity in the ventral striatum and the RT costs for social stimuli, while no such correlation was found for nonsocial stimuli. Interestingly, evidence from a previous study from our lab suggests that the activity of the ventral striatum can be related to the hedonic experience of social stimuli (Schilbach *et al.*, 2010). Other studies have similarly suggested that the ventral striatum is part of a network for the subjective valuation of rewards from a range of different domains (Peters and Buchel, 2010). Our finding might, therefore, be taken to imply that the production of an incongruent response to a gaze shift is all the more time consuming, the more the perception of the face recruits reward-related neurocircuitry possibly related to pleasant feelings (Rolls *et al.*, 2008).

CONCLUSIONS

Our findings demonstrate that social context significantly influences the neuronal bases of action control. This becomes evident in light of a statistical interaction observed for incongruent actions generated in response to social stimuli. Here, a differential recruitment of sub-cortical structures, previously implicated in motor release mechanisms, implicit learning and reward-related processing was observed. A differential increase of neural activity was also found in inferior frontal, anterior cingulate and dorsal medial prefrontal cortex, brain regions known to be involved in action monitoring, response inhibition and internally oriented cognition. These brain regions are not only known to show interaction effects for cognitive and motivational aspects of response inhibition, but are also part of the VAN which allows for a reorienting response that may be particularly relevant in social contexts.

In light of the discussed parallels between SRC and antisaccade paradigms, we also suggest that our paradigm could be used to study psychiatric disorders that have been investigated using 'classical' antisaccade paradigms, such as schizophrenia, to assess how performance of incongruent actions might be modulated by stimulus type, but also response modality. Similarly, our paradigm might be useful to investigate the effects of 'social gaze' on action control in attention-deficit hyperactivity disorder or autism, disorders that are characterized by impairments of response control and social perceptual difficulties.

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