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Effects of timing and movement uncertainty implicate the temporo-parietal junction in the prediction of forthcoming motor actions

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Abstract

The concept of predictive coding supposes the brain to build predictions of forthcoming events in order to decrease the computational load, thereby facilitating efficient reactions. In contrast, increasing uncertainty, i.e., lower predictability, should increase reaction time and neural activity due to reactive processing and believe updating. We used functional magnetic resonance imaging (fMRI) to scan subjects reacting to briefly presented arrows pointing to either side by pressing a button with the corresponding index finger. Predictability of these stimuli was manipulated along the independently varied factors “response type” (known hand or random, i.e., unknown order) and “timing” (fixed or variable intervals between stimuli).

Behavioural data showed a significant reaction-time advantage when either factor was predictable, confirming the hypothesised reduction in computational load. On the neural level, only the right temporo-parietal junction showed enhanced activation upon both increased task and timing uncertainty. Moreover, activity in this region also positively correlated with reaction time. There was, however, a dissociation between both factors in the frontal lobe, as increased timing uncertainty recruited right BA 44, whereas increased response uncertainty activated the right ventral premotor cortex, the pre-SMA and the DLPFC. In line with the theoretical framework of predictive coding as a load-saving mechanism no brain region showed significantly increased activity in the lower uncertainty conditions or correlated negatively with reaction times. This study hence provided behavioural and neuroimaging evidence for predictive motor coding and points to a key role of the right temporo-parietal junction in its implementation.

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Keywords

fMRI; Reaction time; Parietal; Frontal; Hand; Movement

Introduction

Motor responses to an incoming, e.g. visual, stimulus require several sequential processes to take place, such as stimulus perception, motor program selection, preparation and, finally, movement initiation including the correct timing of its execution (Goodale and Humphrey, 1998; Rizzolatti et al., 1998; Desmurget et al., 1999; Gentilucci et al., 2000; Lloyd et al., 2003).

To enable a more economic processing of incoming stimuli and a more efficient reaction the brain may decrease the computational load by using the principle of predictive coding (Mehta, 2001; Summerfield et al., 2006; Kilner et al., 2007b). Predictive coding refers to a hypothesis on the fundamental nature of information processing in the (human) brain. The key idea formulated in several theoretical papers and increasingly supported by experimental findings is, that the brain does not passively process information received from its environment but rather builds a priori models of these and their underlying causes (Rao and Ballard, 1999; Mehta, 2001; Hosoya et al., 2005; Kilner et al., 2007b; den Ouden et al., 2008). These omniscient and multi-layered predictions are then applied for neuronal inferences that ultimately lead to perception and behaviour. This theory hence conceptualise the brain as a “Bayesian machine”, which derives precepts from a combination of its input and priors which are based on previous information, i.e., learning. The behavioural advantages of such a mechanism are obvious. On one hand, correct predictions entail a considerable reduction in computational load, as incoming information only has to be compared against expectations rather than being analysed from scratch. On the other hand, based on appropriate weights on different priors (which themselves represent another set of priors in a hierarchical scheme of predictions) ambiguous information can be dealt with more efficiently, allowing inferences not be possible on the information alone. To date, this concept, which is immanently linked to implicit learning, has been discussed in more detail in recent studies investigating visual decision-making tasks. These showed that different task sets, (i.e., predictions) bias the processing of incoming stimuli (Summerfield and Mangels, 2006; Summerfield et al. 2006). Predictive coding, however, should not be restricted to perceptual tasks. A good example for a corresponding bias in the motor domain is found in go/no-go oddball tasks (Casey et al., 1997; Bokura et al., 2001; Menon et al., 2001; Watanabe et al., 2002). Here, a prepotent response towards the more frequently required action is established by either implicit learning or, more commonly, by an explicit instruction. Behaviourally this prepotency, i.e., prediction, is evident by faster reaction times and reduced errors in responding to the predominant trials as opposed to the rare deviant events. Mechanistically, these effects might be attributable to a reduction of computational load in areas related to motor preparation enabled by the prediction of forthcoming events and their associated responses. In particular, the gain in efficiency can be explained by the fact that due to predictive coding areas involved in stimulus perception and motor preparation only have to confirm that the prepared response is indeed appropriate for the current stimulus, rather than choosing a response de-novo from the motor repertoire.

In order to delineate the cortical areas responsible for these mechanisms, we investigated the neural correlates of predictive motor coding using an indirect approach. In particular, the amount of predictability and hence possible pre-selection was manipulated by modulating the uncertainty of the required response. In a context of high uncertainty predictions will rarely be met, resulting in a high prediction error, increased ad-hoc processing and more frequent updating of believes (Behrens et al., 2007). The theoretical basis for this increased demands on believe updating is that all priors are themselves subject to constant change based on the incoming information, shaping a dynamical system comprising the constant application and modification of a priori expectations. The dynamics of this adaptation are primarily driven through the prediction error resulting from comparing the input to previous priors (Kilner et al., 2007b). If the latter provided a reliable representation of the environmental, i.e., if prediction error was small, the structure of the prior is reinforced. In case of a large prediction error, however, the current structure of the priors apparently does not provide a valid prediction of incoming information. Consequently, the prior will be updated based on the received input in order to better align further predictions with previous experience. The computational demand of areas engaged in predictive coding should hence be higher if the brain's prediction is not fulfilled (requiring additional processing and updating of priors) as compared to a situation where prior expectations are met. Conversely, they should be less active in conditions, which are well predictable, providing the conceptual basis for the presented experimental approach. Areas sustaining predictive motor coding should hence be discernable by comparing conditions involving a high amount of uncertainty (as understood in information theory) to those where uncertainty is low or absent. In particular, based on the theoretical framework outlined above, areas involved in predictive motor coding should feature a significant higher activation in conditions involving higher uncertainty about a subsequently required movement announced by an external stimulus. In order to gain additional insight into the composition of the cortical motor prediction system, we also examined whether separate brain loci are responsible for coding the required response type, i.e., motor preparation, and the required response timing, i.e., movement execution, respectively. That is, are there areas, which are more active during high uncertainty about the required response (i.e., benefit from predictions about the response type), while others are more active during high uncertainty about response timing (i.e., benefit from predictions about the correct timing)?

This question was addressed by a functional magnetic resonance imaging (fMRI) study, in which subjects had to respond to visually presented arrows by pressing a button with the corresponding hand. In this experiment, the predictabilities of both the required response type (left/right hand) and its timing were varied independently of each other in a two-factorial experimental design, and set-related changes in fMRI signal were compared as a marker of neuronal activity.

In particular we investigated whether a potential predictive motor coding is implemented by the “classical” premotor areas, such as dorsal premotor cortex or pre-supplementary motor area (Cunnington et al., 2006) or by areas associated with integration and processing of incoming stimuli, such as the inferior parietal lobe (Toni et al., 2002) or the right temporo-parietal junction (Decety and Lamm, 2007).

Materials and methods

Subjects

We examined 26 healthy volunteers (age range 21 to 59 years, mean age 37 years; 12 females) without any record of neurological or psychiatric disorders and normal or corrected-to-normal vision. All subjects gave informed written consent to the study protocol, which had been approved by the local ethics committee of the University of Cologne. Right-hand dominance of the participants was established by means of the Edinburgh handedness inventory (Oldfield, 1971), which yielded a mean laterality quotient of 93.8 (SD: 7.7).

Experimental protocol

The task was to react as fast and correctly as possible to arrows pointing to either side, which were presented briefly (200 ms) in the central field-of-view. Responses consisted of pressing a button on a MRI-compatible response pad (LumiTouch, Burnaby, Canada) with the corresponding index finger. As this study aimed at analyzing the neural correlates of changing uncertainty in movement timing or direction, the direction of the arrows (left/right/random) and their inter-stimulus interval (ISI, which could be fixed or jittered) was systematically varied as described below. All visual stimuli were presented using the "Presentation" software package (Version 11.0, Neurobehavioral Systems Inc., Albany, CA/USA) 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 (14°×8° viewing angle). In the experiment, task blocks of 40.8 s duration were periodically alternated with rest periods ("baseline") lasting 22.5 s. Each task block started with a 3 s instruction, which informed the subject which of the following six experimental conditions had to be performed in the upcoming block:

Right hand – fixed ISI (Rf)/left hand – fixed ISI (Lf)

In these conditions arrows pointing to only one side were presented, that is, the subjects knew the required movement beforehand. Moreover, the stimuli followed each other by a fixed ISI of 700 ms (i.e., a stimulus onset asynchrony [SOA] of 900 ms, given 200 ms stimulus duration) cueing the participants to anticipate the required response timing. Consequently, in the Rf and Lf conditions, both direction and timing were known a priori by the subjects, rendering uncertainty minimal.

Right hand – jittered ISI (Rj)/left hand – jittered ISI (Lj)

These two conditions matched the previous ones with respect to the predictability of movement direction, as again actions by only one hand was required during any given block. However, in contrast to the Rf/Lf conditions, the ISI was now randomised between 600 and 800 ms (mean ISI: 700 ms matching the "fixed" conditions, jitter uniformly distributed). This modification hence made the required timing uncertain and disallowed stimulus anticipation. Consequently, during the Rj/Lj blocks the subjects knew a priori the hand they would be using in the upcoming event but not when the response had to be executed.

Random “both” hands – fixed ISI (Bf)/random “both” hands – jittered ISI (Bj)

In contrast to the previous conditions, the two “random hands” tasks required the subjects to react to arrows, which randomly pointed to either side with a probability of 50% each. Therefore, subjects did not know whether the next trial required a response with the left or right hand, resulting in increased uncertainty about the required movement direction. As in the unilateral context, the stimulus timing was again modulated between the two conditions Bf (fixed ISI of 700 ms) and Bj (ISI jitter uniformly distributed between 600 and 800 ms, mean 700 ms).

Regardless of the condition, each task block consisted of 42 individual stimuli. In the course of the entire experiment, each of the six conditions was repeated in four individual blocks. The order of the ensuing 24 blocks was pseudo-randomised and counterbalanced across subjects.

Behavioural data analysis

The behavioural measurements taken during the fMRI experiment were analysed off-line using MATLAB (MathWorks, Natick, MA). The effect of the experimental factors (movement certainty: unilateral/ random; response timing: jittered/fixed) on mean reaction time and percentage of correct responses were compared by a repeated measurement analysis of variance (rmANOVA). If the effect of a factor was significant, pairwise comparison was performed by a post-hoc T-test ($p<0.05$, corrected for multiple comparisons using Tukey's procedure for balanced ANOVAs).

Functional magnetic resonance imaging

Images were acquired on a Siemens Trio 3 T whole-body scanner (Erlangen, Germany) using blood-oxygen-level-dependent (BOLD) contrast (gradient-echo EPI pulse sequence, TR=1.6 s, TE=30 ms, flip angle=90°, in plane resolution=3.1×3.1 mm, 26 axial slices (3.1 mm thickness) covering a region extending from prefrontal (rostral) to visual cortex (caudal). The cerebellum and anterior temporal cortices, however, were outside the field-of-view. Image acquisition was preceded by 4 dummy images allowing for magnetic field saturation. These were discharged prior to further processing. Images were analysed using SPM5 (www.fil.ion.ucl.ac.uk/spm). First, the EPI images were corrected for head movement 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 normalised to the MNI single subject template (Holmes et al., 1998) 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 2×2×2 mm^3 voxel size. The normalised images were spatially smoothed using an 8 mm FWHM Gaussian kernel to meet the statistical requirements of the General Linear Model and to compensate for residual macroanatomical variations.

Statistical analysis

The fMRI data was analyzed using a general linear model as implemented in SPM5. Each experimental condition was modelled using a boxcar reference vector convolved with a canonical hemodynamic response function 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 to a second-level group-analysis using an ANOVA (factor: condition, blocking factor subject; Penny and Holmes, 2003) employing a random-effects model. In the modelling of variance components, we allowed for violations of sphericity by modelling non-independence across images from the same subject and allowing unequal variances between conditions and subjects as implemented in SPM 5. The mean reaction times for each subject and condition were included as covariates into the same model in order to separate task-related from performance-related activity. More precisely, the reaction times obtained from each subject in each condition were modelled by their level-specific interaction with the main regressors reflecting the separate conditions. This entailed the construction of six covariate regressors, each reflecting the recorded reaction times in one of the experimental conditions. Within each regressor, i.e., condition, the covariate was mean-centred, and hence reflected only those variations in reaction time that occurred within each main effect. The regression for reaction-time differences was hence orthogonal to the main effects of the different tasks and reflected variability in behavioural performance within this condition. This design therefore allowed to test for the neuronal activations evoked by the different tasks (and differences thereof) independently of those effects that were related to the observed variations in reaction time.

Simple main effects of each task (vs. the resting baseline) as well as comparisons between experimental factors were tested by applying appropriate linear contrast to the ANOVA parameter estimates. Composite main effects (e.g. activations, which were present in each of two different conditions, e.g., left or right-handed responses to jittered stimuli, $Rj \cap Lj$) were tested by means of a conjunction analysis. The resulting SPM(T) maps were then thresholded at $p<0.05$ (cluster-level FWE corrected; cluster-forming threshold at voxel-level $p<0.001$; Worsley et al., 1996) and anatomically localised using version 1.5 of the SPM Anatomy toolbox; www.fz-juelich.de/ime/spm_anatomy_toolbox, Eickhoff et al., 2005, 2006, 2007).

Results

Behavioral data

Mean reaction times and percentages of correct responses are summarised in Fig. 1. We found significant ($p<0.05$) main effects of both experimental manipulations (response type/timing uncertainty) on the reaction times, as well as a significant interaction between these. By contrast, there was no significant main effect of hand (i.e., left- and right-hand responses). Post-hoc pairwise *T*-tests revealed significantly ($p<0.05$, corrected) slower reaction times due to uncertain timing in the unilateral conditions, independently of which hand was used (Lj vs. Lf, Rj vs. Rf). Comparing the reaction times obtained during blocks where the response direction was uncertain (Bf, Bj) with those where the required hand was known a priori yielded significant slower reaction times in the uncertainty conditions. The difference between jittered and fixed presentation of random stimuli (Bf vs. Bj), finally, was not significant. In summary, subjects were fastest when they knew the required type and timing of their action, significantly slower when the stimuli were presented in a jittered fashion and slowest, when they could not prepare for a particular movement, with no effect of timing uncertainty in the latter condition.

With respect to the percentage of correct answers, we found a significant main effect of response uncertainty, with more errors in the uncertain conditions Bf and Bj. The main effect of timing uncertainty and the interaction between both factors, however, was not significant.

Imaging data – baseline contrasts

Right-hand movements (independent of timing: Rf∩Rj, Fig. 2a) activated left primary motor (M1/Areas 4a and 4p) and somatosensory (S1/Areas 3b, 3a, 1, 2) cortices, thalamus and insula. Bilateral activation was found in the secondary somatosensory cortices (SII/Areas OP 1 and OP 4), basal ganglia, supplementary motor area (SMA/Area 6), dorsal (dPMC/Area 6) and ventral (vPMC/Area 6, encroaching Area 44) premotor cortices. Right-sided activation was observed in inferior parietal cortex (IPC/Areas PFm and PGa), temporo-parietal junction (TPJ, Area PF) and middle frontal gyrus. As expected, left responses (Lf∩Lj, Fig. 2b) produced a virtually mirror-reversed pattern of activity. In the random hand conditions (Bf∩Bj, Fig. 2c) we found bilateral activation in primary sensory-motor cortices, putamen, pre-supplementary and supplementary motor areas, ventral premotor cortex, cingulate motor cortex as well as the intraparietal sulcus (extending onto the SPL) and temporo-parietal junction (Area PF). Right-hemispheric activation was observed in the right inferior frontal gyrus (BA 44) and lateral prefrontal cortex.

In order to identify regions that are consistentlyactive throughout all conditions, i.e. areas involved in responding to visual stimuli independently of the active hand and the uncertainty factors (“core motor areas”) we performed a conjunction analysis over all sixconditions (Fig. 2d). This analysis revealed that three regions in premotor Area 6 (corresponding to the dorsal premotor cortex on both hemispheres [MNI-coordinates: −44/−4/53 and 50/0/39] and the supplementary motor area [MNI-coordinates: 0/−4/65]) as well as the putamen (bilaterally) were consistently activated across all conditions.

Imaging data – effects of response uncertainty

Neuronal effects of increased response (i.e., movement direction) uncertainty were localised by contrasting activation in the blocks where arrows were presented in a randomised fashion to those where subjects knew that they had to respond only with either hand [(Bf+Bj>Rf+Rj) ∩(Bf+Bj>Lf+Lj), Fig. 3]. This analysis revealed, that uncertainty about the subsequent movement resulted in increased activation of the pre-SMA (BA 6; −6/12/47), and bilaterally in the superior frontal gyrus (anterior to BA 6; 36/−2/55 and −30/−4/53) and the intraparietal sulci extending onto the SPL (Areas 2, 7A, 7PC, hIP3; −34/−44/58 and 36/−48/65).

Increased activation due to movement uncertainty was also observed in several right-hemispheric areas, in particular the temporo-parietal junction (Area PF; 60/−38/15), the dorso-lateral prefrontal cortex (DLPFC, middle frontal gyrus; 28/50/15) and the ventral premotor cortex (vPMC, between BA 6 and BA 44, 40/4/33).

The reverse contrast testing for areas with increased activity in the unilateral conditions did not areas of significantly enhanced neural activity.

Imaging data – effects of timing uncertainty

As noted above, a significant difference in reaction times between fixed and jittered stimulus onset was found only for the unilateral conditions. Consequently, neuronal effects of increased timing uncertainty were localised by contrasting the jittered unilateral conditions to the respective fixed interval blocks. Effects of increased timing uncertainty independently of the used hand [(Rj>Rf)∩(Lj>Lf), Fig. 4] were found at the temporo-parietal junction (Area PF, 60/−38/15) and the right inferior frontal gyrus (BA 44, 56/14/15). Additional hand-specific effects of timing uncertainty, however, were not observed. In particular, testing for an interaction between response hand (left/right) and onset timing (fixed/jittered) did not reveal any significant activation.

Moreover, no region was associated with reduced timing uncertainty, i.e., showed increased activation in the fixed interval condition relative to those with jittered onset. This was true both when testing for the main effect of “jittered — fixed” as well as for separated analyses of only left and right-handed conditions, respectively. Finally, in accordance with the absence of behavioural effects between the jittered and fixed presentations of “random hand” trials, the contrasts Bf>Bj and its reverse (Bj>Bf) did not yield any significant difference in neuronal activation associated with a timing (un-)certainty in the context of concurrent uncertainty on the required response.

Imaging data — comparison of uncertainty effects

Comparing the increased activation due to uncertain timing and uncertainty about the required response, respectively, revealed that both factors engage a similar region at the border between the inferior parietal cortex and the temporal lobe. A conjunction analysis between the effects of increased response and timing uncertainty confirmed, that indeed only a single focus at the temporo-parietal junction (Area PF, 60/−38/15) was increasingly active when predictive coding on upcoming response requirements was impeded. In contrast, the two regions around the inferior frontal gyrus showing increased activation in the analyses detailed above were separated from each other. This dissociation pertained to the functional specificity of the observed activations as well as to their anatomical location (BA 44 vs. vPMC, cf. Fig. 5).

Imaging data — reaction-time correlation

To further assess the role of different brain areas in the context of predictive coding for upcoming motor outputs, we also tested, within the same GLM, for correlations between neuronal activity and the reaction times as measured during fMRI scanning. These behavioural measures serve as surrogate measures of processing speed and hence computational load. As the reaction-time regressors were orthogonalised by condition to the respective main effects, this analysis only aimed at identifying neuronal correlates of reaction-time differences independent of the experimental main effects. Testing for the main effect of increased reaction time, i.e., searching for areas that are more active when subjects took longer to react, again revealed a significant activation at the temporo-parietal junction (Area PF, 62/−38/15). As summarised in Fig. 6, activation in this region was therefore not only associated with increased response and timing uncertainty but also (throughout all conditions) with slower reaction times, i.e., higher computational load.

Condition specific differences in these reaction-time effects (equivalent to a varying slope of the covariate regression between conditions) were not observed. That is, correlations of neuronal activity with increased reaction times were found consistently and exclusively in the ventral part of Area PF covering the temporo-parietal junction. Likewise, we did not find any region, which showed a significant negative correlation with processing speed, i.e., was more active when subjects responded faster.

Discussion

We investigated the putative neural substrates of predictive motor coding by modulating the uncertainty about the required response and its timing using fMRI. We found that only the temporo-parietal junction (ventral Area PF) showed enhanced activity when uncertainty was increased along either dimension. Moreover, the same region also featured a significant correlation with longer reaction times, i.e., increased computational load. There was, however, a dissociation between both factors in the frontal lobe. Increased timing uncertainty recruited right BA 44, whereas increased response uncertainty was associated with higher activity in the right ventral premotor cortex (posterior–dorsal to BA44), the pre-SMA and the right DLPFC.

Core motor areas

“Core motor areas” refers to regions in the basic network activated throughout all conditions (identified by a conjunction analysis, cf. Fig. 2d), i.e., the bilateral dorsal premotor cortex, the supplementary motor area and the putamen.

In non-human primates, neurons in the dorsal premotor cortex (dPMC/F2) link spatial encoding of targets with movement plans and implement stimulus–response-mapping in the context of reactive behaviour (Luppino et al., 2003). A homologous role for human dPMC was shown in a recent meta-analysis of functional neuroimaging studies (Chouinard and Paus, 2006). Lesion studies (Petrides, 1982; Halsband and Passingham, 1985) as well as transcranial magnetic stimulation experiments (Chouinard et al., 2005) also support an essential role for dPMC in associating arbitrary cues to motor responses. We would hence argue that the observed bilateral activation of dPMC (anatomically assigned to BA 6 using probabilistic cytoarchitectonic maps) is attributable to maintaining the (arbitrary) mapping between visual stimuli and the instructed motor response.

The supplementary motor area (SMA), on the other hand, has repeatedly been implicated in the initiation of movements (Cunnington et al., 2003). For example, in macaques projections between Areas F3 (SMA) and F1 (M1) are activated just prior to movement execution (Luppino et al., 2003; Myers and Mackinnon, 2004). A recent effective connectivity study in humans (Grefkes et al., 2008a) supports this notion by revealing that SMA exerts strong context-specific influence on M1: during unilateral hand movements, SMA promotes ipsilateral and suppresses contralateral M1 activity indicating a dynamic role of the SMA in the initiation and top-down control of actions. Disruption of these interactions by stroke is associated with poor motor performance (Grefkes et al., 2008b).

The putamen and more generally the basal ganglia, finally, are well-established constituents of cortical-subcortical loops for movement preparation (Jueptner and Krukenberg, 2001; Middleton and Strick, 2000). Furthermore, several studies lead to the notion that the basal ganglia are an essential component for mental timekeeping mechanisms, as a disruption of these structures produces deficiencies in estimating temporal intervals (Maricq and Church, 1983; O'Boyle et al., 1996; Pastor et al., 1992).

Areas specifically recruited by response uncertainty

Increasing activity in “random hand” conditions was observed just anterior to the SMA, i.e., in the pre-SMA. In their review, Picard and Strick (1996) argue for an important role of the pre-SMA in tasks requiring higher motor control such as motor selection or inhibition (cf. Mostofsky and Simmonds, 2008). This assumption is supported by its connectivity pattern in non-human primates. Here, pre-SMA receives afferences from the inferior parietal lobule (IPL, Luppino et al., 1993) supplying it with integrated sensory input and motor plans, and projects predominantly to the dPMC. As the “random” conditions require a stimulus contingent release of motor plans, the observed pre-SMA activation may reflect increased demands in motor control evoked by the uncertainty about the subsequent movement.

Uncertainty about the subsequent movement direction also elicited activation of the right ventral premotor cortex (vPMC). These observations are in line with Kurata (2007), who observed vPMC activation related to the transformation of incoming sensory input into hand movements. Moreover, several studies have demonstrated that lesions of this region produce impairments in matching motor act with sensory inputs (Rizzolatti et al., 1983; Kurata and Hoshi, 1999). In the unilateral conditions, however, transformations were necessary to a lesser degree, as subjects knew the movement direction a priori and could hence use the stimuli primarily as a go-signal. The observed activation may thus reflect increased demands for integration between sensory inputs and hand movements in the uncertain condition as previously hypothesised by Manthey et al. (2003).

Many functions have been attributed to the dorso-lateral prefrontal cortex (DLPFC). For example, Yamaguchi et al. (2008) concluded from activation in a go/no-go task that right DLPFC acts as a core node in the response inhibition network. Shallice (2004) proposed that this region is generally involved in the executive control of the motor system, a hypothesis that was supported by Vogt et al. (2007) who found activation of the right DLPFC when newly configured motor plans had to be executed. As shown by our behavioural data, the subjects reacted slower and less correct, when the movement direction was unknown. Consequently, the demand for action monitoring and executive supervision should be increased. We would hence propose that, in line with previous experiments, the increased

DLPFC activation in the “random hands” condition reflects higher demands for the cognitive control of task performance.

Unfortunately, there is no unambiguous attribution of the bilateral cluster on the superior frontal gyrus just anterior to BA 6 (36/−2/55,−30/−4/53). The location of this activation might correspond to the rostral portion of the dorsal premotor cortex (pre-dPMC; Boussaoud et al., 2005). This area was implicated in stimulus–response-linkage in an implicit learning task (Grafton et al., 1998) as well as activated during sequential updating of verbal or spatial mental representations in response to sensory cues (Hanakawa et al., 2003; Tanaka et al., 2005). According to the concept of predictive coding, activation of pre-dPMC in the random condition may therefore reflect more frequent updating of predictions. However, increased visual exploration of the presented arrows in the random condition by saccadic eye movements cannot be ruled out in the current study, so that activation on the posterior end of the superior frontal gyrus may also reflect an eye movement confound. That is, the activated area could very well also correspond to the frontal eye field (FEF) which represent the principal region involved in oculomotor control and saccade generation (Paus, 1996; Picard and Strick, 2001).

Areas specifically recruited by timing uncertainty

Specific activations in the context of timing uncertainty were observed in right BA 44 (Amunts et al., 1999). As summarised by Binkofski and Buccino (2004), there is strong evidence for homology between human BA 44 and the rostral ventral premotor cortex (r-vPMC/Area F5) in other primates. It has been described, that in primates F5 bilaterally contributes to the selection of specific action patterns from the motor repertoire (“vocabulary of motor actions”) and their time-specific forwarding to other premotor areas. In contrast, the function of human BA 44 shows a marked hemispheric differentiation: left BA 44 (Broca's Area) is a core area of the cortical speech production and language network (Price, 2000; Friederici, 2006; Heim et al., 2007). The function of right BA 44, however, is less well understood. Previous studies on rhythmic tapping (Zatorre et al., 1996) have implicated this region in movement timing and the production of rhythmic movements. In particular, it has been suggested that activation of right Area 44 is associated with the retrieval and rehearsal of auditory information, which in turn could provide the basis for rhythmically timed movements (Rao et al., 1997). For example, Hinton et al.(2004) showed that counting, but not interval timing, strongly activated right Broca's Area, indicating that the aforementioned retrieval and rehearsal may rely on (subverbal) counting. Hanakawa et al. (2008) reported that preparation, execution and imagery of sequential finger tapping all activate right Area 44 pointing towards a rather generic role of this region in sequence production. Our data showed activation in right Area 44 which was significantly increased in the context of jittered, i.e., unpredictable, stimulus timing. Following the notion that Area 44 is engaged in interval timing and rhythm generation, increases in activation may reflect disturbed automatisation processes since the temporal jitter makes establishing of a continouous rhythm impossible. Such reduced automatisation would in turn entail higher processing demands of timekeeping mechanisms, which again is in line with a Bayesian perspective in which predictive, e.g., rhythmic, events are anticipated in order to reduce the computation load.

A different view on the role of Area 44 in movement preparation, however, has been provided by lesion studies regarding this region showing disruption of normal processing in a stop signal task, i.e., resulting in disturbed inhibition of motor acts (Aron et al., 2003). In the same vein, Chambers et al. (2006) demonstrated that TMS over right BA 44 impairs in the ability to stop an initiated motor action (but not movement execution *per se*). Finally, based on an fMRI study comparing the inhibition of imitative and over-learned responses, Brass et al. (2005) concluded that BA 44 generates stop signals for action control (cf. Rubia et al., 2001). In the light of these findings, we propose that the observed activation in right BA 44 might relate to a hold-and-release function of this region. Since subjects could roughly estimate the time of next trial but were instructed to react only once the arrow was presented, they may have prepared the correct (known) movement beforehand, withholding it until the cue. Following the notion raised in the abovementioned studies, BA 44 would hence serve as an “executive brake” in these conditions, holding back the prepared response until the go-signal appears (Konishi et al., 1999). This interpretation also explains why BA 44 was not activated when contrasting uncertain vs. certain timing of random stimuli: in neither of these conditions, the correct action could be prepared and put on a hold-release mode since the required movement was indicated by the stimulus.

Predictive coding in the motor system

Predictive coding postulates that the brain uses previous information for building predictions of forthcoming events in order to minimise computational load and to enable decisions in uncertain environments (Creutzig and Sprekeler, 2008). To this end, predictions are compared against the actual sensory input, resulting in a prediction error if the brain's predictions are not fulfilled. It is important to note that from a theoretical perspective predictive coding does not depend on the subjects using an explicit anticipatory strategy as they might do if there was a behavioural advantage from guessing the upcoming event. Likewise, predictive coding as a computational mechanism also does not postulate a conscious engagement of the subjects in an active comparison of expectations and new input. Rather, most theories on predictive coding conceptualise this mechanism as an unconscious and highly automated process, representing a basic feature of neuronal computing as opposed to a voluntary cognitive process (Kilner et al., 2007b). That is, the terms predictive coding refers to a hypothesis on how the brain may handle its demands rather than a voluntary strategy used by the subjects. In this context, it is also important to re-emphasise that putatively the most important role of predictive coding is to structure and conceptualise the environment in order to facilitate perception and decision making. The activity in areas participating in these processes can therefore be assumed to be predominantly influenced by the validity of the environment (Courville et al., 2006) and largely independent from the person's subjective sense of uncertainty (though the later may probably arise from it). From these theoretical considerations, it follows that predictive coding does not inevitably need to represent a behavioural advantage. Hence, it should not be conceptualised as an explicit “strategy” for guiding one's behaviour. In fact, such voluntary anticipation can virtually be excluded in the case of response uncertainty. Since the stimuli in these conditions were presented randomly with a probability of 50% each, they represented a situation of total uncertainty about the upcoming stimulus. That is, the subjects had no behavioural advantage if they would have tried to anticipate an upcoming stimulus and should hence not have engaged in conscious anticipation or preparation.

Given the dynamic nature of predictive coding, a prediction error will then entail an adjustment of the predictions by incorporating the sensory data into subsequent predictions. The minimisation of prediction errors hence results in an adjustment of neuronal representations for improved accuracy of future predictions (Summerfield et al., 2006; Summerfield and Mangels, 2006; Kilner et al., 2007a). It becomes apparent, that in the context of high uncertainty predictions will rarely be met resulting in frequent prediction errors and constant updating of believes (Behrens et al., 2007). Therefore, activity in areas sustaining predictive coding should have a higher computational load under situations of increased uncertainty and hence become more active in the fMRI measurements. While this mechanism provides the conceptual framework for the present study, it must be acknowledged, that in a constantly uncertain environment the confidence in prior prediction may gradually decrease. In a hierarchical Bayesian scheme, such reduced confidence would be governed by higher-level priors that represent the volatility of the environment and adapt the variance (i.e., confidence) of lower-level expectations. In spite of these theoretical considerations, experimental data on the neuronal representation of volatility and hence the hierarchical organisation of prior expectations and believes is yet sparse and predominantly limited to decision making (Behrens et al., 2007). In order to maximise the detection power in the contrast of high vs. low uncertainty situations, the present experiment used a block-design involving rather short sequences of both conditions separated by resting baseline.

Predictive coding and motor preparation

So far, however, evidence for predictive coding was mainly demonstrated in the context of sensory paradigms. Summerfield and Mangels (2006) reported that the quality of encoding rises when items were predictable due to a pre-allocation of attentional resources. Similarly, behavioural recording and neuroimaging data suggested that the brain might resolve perceptual ambiguity by anticipating forthcoming stimuli and matching sensory input against a template of predictive codes. Hereby sensitivity is increased in the presence of noise but perception is also biased towards what is anticipated a priori (Summerfield et al. 2006). However, predictive coding also should be a crucial component of motor preparation, where it should allow to pre-select motor programs based on a prediction of future events and the hereby-necessitated movements. If an upcoming stimulus matches the anticipation, the response is already prepared and can be executed immediately. The reduction in computational load by successful predictions should hence decrease reaction times while unsuccessful ones require reactive stimulus processing and updating of assumptions due to prediction error. Consequently, reaction times should be higher when predictions are met less often, which was confirmed in the current study, when movement latencies were compared between the certain (predictable) and uncertain conditions. The fMRI data showed that this behavioural difference was associated with increased activation of the temporo-parietal junction (TPJ, Area PF; Caspers et al., 2006, 2008). In particular, activity in this region was higher when uncertainty about either the nature of the subsequent movement or its timing was increased. Importantly, enhanced BOLD signal was positively correlated with reaction time across all experimental conditions. That is, all three analyses (effects of timing uncertainty; effects of response uncertainty and positive reaction-time correlation) point to a role for the TPJ in sustaining computations related to uncertainty processing. Hence, these results indicate that increased TPJ activity is related to additional processing caused by unsuccessful anticipation, which from Bayesian perspective would entail a higher prediction error. Based on these results, we suggest that the TPJ might play an important role in predictive motor coding. While the exact nature of the sustained computational processes cannot be inferred from the present data, potential functions of this region may involve the updating of action expectations and/or the comparison of pre-prepared programs with the current requirements. This hypothesis is in line with the previously described role of TPJ in generating, testing and correcting internal predictions about external sensory events in social cognition (Decety and Lamm, 2007). Studies of Corbetta and Shulman (2002) and Downar et al. (2000) enforce our hypothesis, as these authors observed activation of the TPJ region during disruptions in expectation about incoming visual stimuli (i.e. increasing prediction error) or detection of sensory changes in the environment (i.e. updating the present prediction).

Reaction time and frontal activity

Our analysis did not detect brain regions that were more activated in “certain” versus “uncertain” conditions nor regions inversely correlating with reaction times. These findings are well in line with the theoretical framework outlined above: situations where the subsequent stimulus and hence its associated response can be predicted beforehand should feature a decrease in computational load in the whole system. By contrast, previous PET (Hazeltine et al., 1997; Honda et al., 1998) and fMRI studies (Aizenstein et al., 2004; van der Graaf et al., 2006) reported negative correlations between brain activation and reaction times. These studies employed a serial reaction-time task in order to delineate the neuronal networks for implicit and explicit learning. If a particular part of a sequence was previously learned, decreasing reaction times (as a predictor for successful learning) were accompanied by increasing activity in frontal motor areas. In particular, there was a negative correlation between RT and activity in bilateral SMA and right dPMC. As the current study features only conditions where stimuli are either completely predictable or completely unpredictable, we did not expect learning processes to have a significant influence on our data. Although the absence of negative reaction-time correlations in our paradigm lacking any behaviourally relevant learning process is not surprising, the relationship between predictive motor coding and implicit sequence learning will warrant further investigation.

Movement preparation and attention

Our data hence provides behavioural and neuroimaging evidence for predictive mechanisms in the human motor system and points to a potential role of the temporo-parietal junction in their implementation. It should be noted, however, that this interpretation does not oppose other psychological concepts that may be employed to explain the observed results, most obviously movement preparation and attention. Rather, based on recent advances in conceptual models of Bayesian inference (Yuille and Kersten, 2006) in the brain, we would propose that movement preparation and attention might readily be integrated into the abovementioned account of predictive motor coding. In particular, it has been proposed, that within a hierarchical Bayesian framework (Friston et al., 2006), the prediction error can be conceptualised as the saliency of a stimulus, rendering violation of expectations a fundamental mechanism for the allocation of attention (Fletcher and Frith, 2009; Courville et al., 2006). Likewise, predictive coding may also represent the computational basis for an implicit preparation of the most likely future actions (cf. Kilner et al., 2007a). In this framework, active, i.e., conscious planning of movements could then be implemented as an explicit change of priors on different movements by hierarchically higher centres responsible for voluntary control and multi-sensory integration. The computational mechanisms by which conscious planning of movements, overt shifts of attention or voluntary anticipation of upcoming events are implemented in a more general scheme of hierarchical (predictive) movement coding, however, are yet unresolved as their neurobiological correlates. In particular, establishing the relationships between these aspects of motor control and investigating the neuronal foundations thereof remain to be addressed in further experiments specifically designed to assess the interactions between automated computational mechanisms and conscious behaviour.

Predictive coding and the cerebellum

Despite the missing imaging data concerning the cerebellum in the current study, this regions has been frequently demonstrated to play an essential role in sensorimotor prediction (Blakemore and Sirigu, 2003), especially for building predictions about the actual sensory consequences of an executed motor command. This principle is mainly used in early stages of movement execution in order to maintain accurate performance in case of sensory feedback delays (Miall et al., 1993; Wolpert and Kawato, 1998). Discrepancies between the predicted and actual consequences of the movement are then used to update the prediction and minimise the prediction error. Several lesion studies (Smith et al., 2000; Maschke et al., 2004; Morton and Bastian, 2006) support this view as subjects with cerebellar damage feature impairments at making predictive changes but show no alterations in reactive changes. Referring to predictive coding as described above the cerebellum employs a largely identical “basic Bayesian program” to predict subsequent events. However, since the cerebellum is not part of the “classical” predictive coding framework (Kilner et al., 2007a,b) and the current task does not feature predictive correction of executed motor commands as primary demand, we suggest that activation of this area is (in this context) not plausible. On the other hand the cerebellum is involved in timing processes and assumed to take part in an internal timing system (Harrington and Haaland, 1999). Cerebellar lesion studies support these findings as patients are impaired in precise timing (Ivry, 1996, 1997). Along the lines of the current study, Dreher and Grafman (2002) observed increasing activation of the cerebellum in random relative to fixed timing in a task-switching experiment. Therefore, we suggest that we might have observed cerebellar activation as timing uncertainty increased.

Conclusion and further directions

In the present study, we have provided experimental evidence for the existence of predictive coding mechanisms in the human motor system. In particular, our data showed a significant reaction-time advantage when either the direction or timing of subsequent stimuli were predictable in a serial reaction-time task. This observation is in line with the hypothesised reduction in computational load entailed by sub-conscious predictive coding. The behavioural difference was associated with increased activation of the TPJ under conditions of higher uncertainty. Supporting evidence for an interpretation of the TPJ activation as related to predictive motor coding was provided by the fact that only activity in this region was positively correlated with reaction time, which may be attributable to increased updating of prior expectations entailed by higher uncertainty. An intriguing question that remains to be addressed in further studies is to which degree these potentially generic predictive mechanisms and the preparation of motor acts *per se* overlap in terms of behavioural effects and neural substrates. In other words, can (automated) predictive motor coding be differentiated from (voluntary) movement preparation? Moreover, while we here present evidence for the predictive coding for subsequent actions, these representations should themselves be subject to higher-level priors reflecting, e.g., the volatility of the environment. Testing the behavioural and neural effects of parametrically varied uncertainty and preferentially doing so in a continuous, i.e., not blocked, design may provide a means of assessing this hierarchical structure and hold further insight into the organisation of action preparation. Finally, the interaction between areas implementing predictive coding, those involved in motor execution, and those providing the cognitive control thereof, remains to be investigated in more detail by further experiments in order to gain a better understanding of the cortical networks underlying human motor behaviour.

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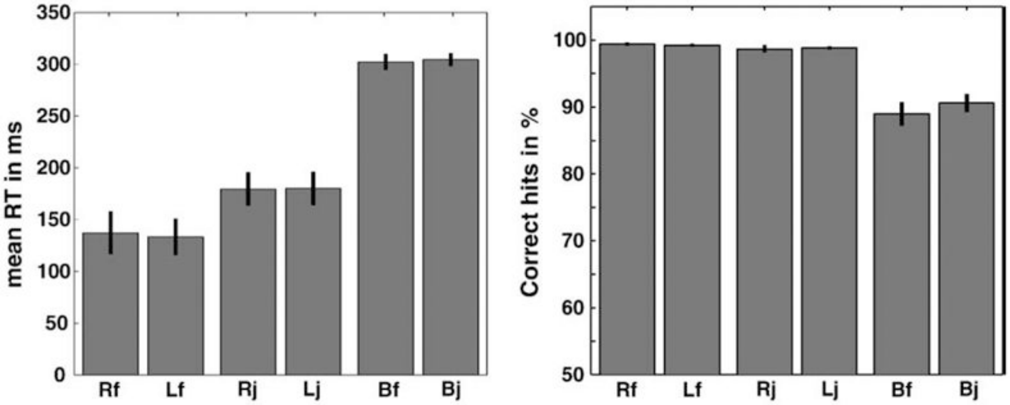

Fig. 1.

Left panel: Mean reaction times for the six experimental conditions. In the unilateral conditions, uncertainty in timing results in significant slower reaction times. Uncertainty of the response type also produced significant slower reaction times. Comparing fixed and jittered presentation of randomly pointing arrows, however, we observed no significant differences in reaction time. Right panel: Mean percentages of correct responses for the six experimental conditions. A significant main effect was only found for response type uncertainty.

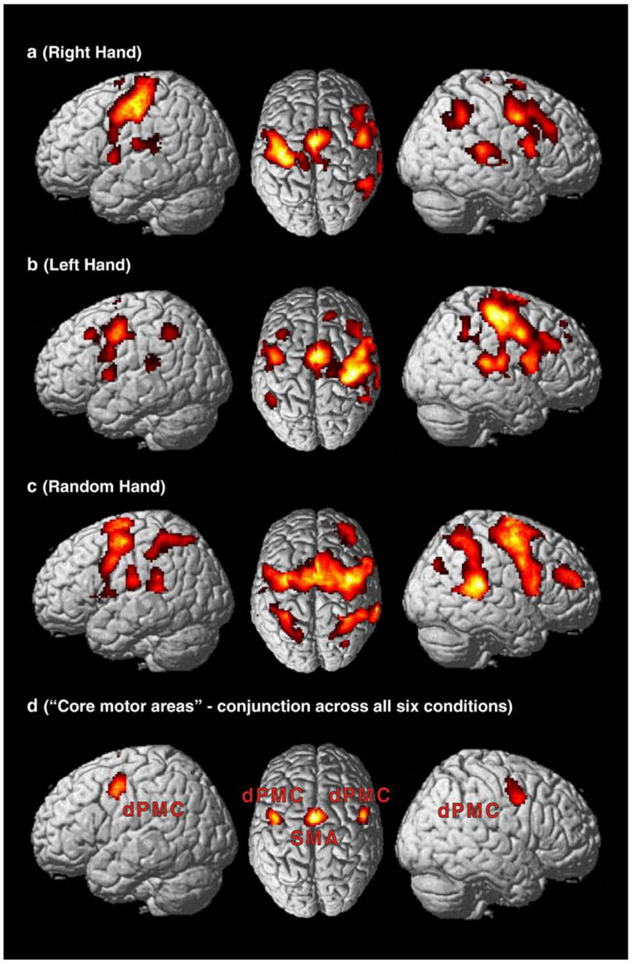

Fig. 2.

(a) Pattern of activation for right-hand movements consisting of left primary motor and somatosensory cortex, thalamus and insula as well as bilateral secondary somatosensory cortex, basal ganglia, supplementary motor area, dorsal and ventral premotor cortices. Furthermore the right temporo-parietal junction and middle frontal gyrus were activated. For left hand movements we found a mainly mirror-reversed pattern of activity (b). Random hand movements (c) feature bilateral activation of the primary sensory-motor and cortex, putamen, pre-supplementary and supplementary motor area, ventral premotor cortex, cingulate motor cortex as well as the intraparietal sulcus and temporo-parietal junction. An additional bilateral cluster is localised on the superior frontal gyrus anterior to BA 6. Right-hemispheric activation was observed in pars opercularis of the right inferior frontal gyrus (BA 44). (d) Areas which have been constantly active throughout all condition and hence represent the "core motor areas". Activity was found bilateral in the dorsal premotor cortex, the mesial aspect of the frontal lobe (SMA) and the putamen.

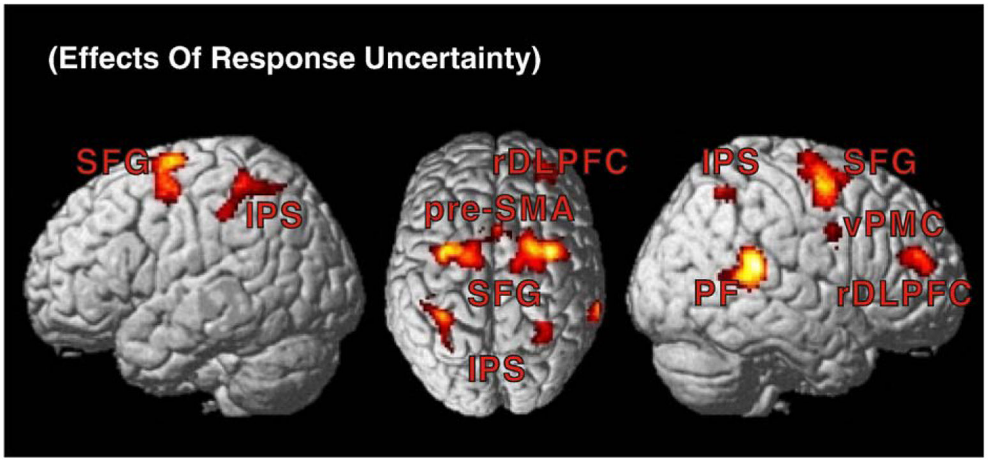

Fig. 3.

Uncertainty about the subsequent movement caused increased activity in bilateral pre-supplementary cortex, superior frontal gyrus anterior to BA6 (SFG) and the intraparietal sulcus. Right-hemispheric activation was observed in the temporo-parietal junction, the dorso-lateral prefrontal cortex and ventral premotor cortex. The reverse contrast (unilateral>random hands) did not yield any significant activations.

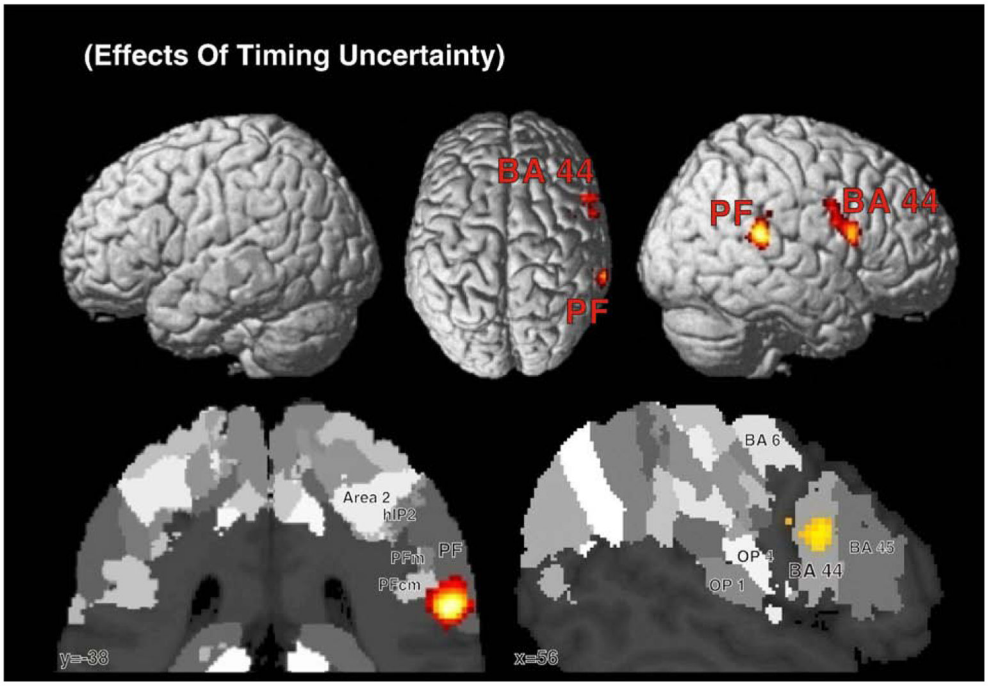

Fig. 4.

The right inferior frontal gyrus (BA 44) as well as the right temporo-parietal junction (Area PF) show increasing activity when contrasting unilateral conditions with fixed and respectively jittered timing. The activated temporo-parietal region (60/−38/15) overlaps with the region activated when contrasting conditions with respectively unilateral and random hand movements (Fig. 3). No region was associated with reduced timing uncertainty.

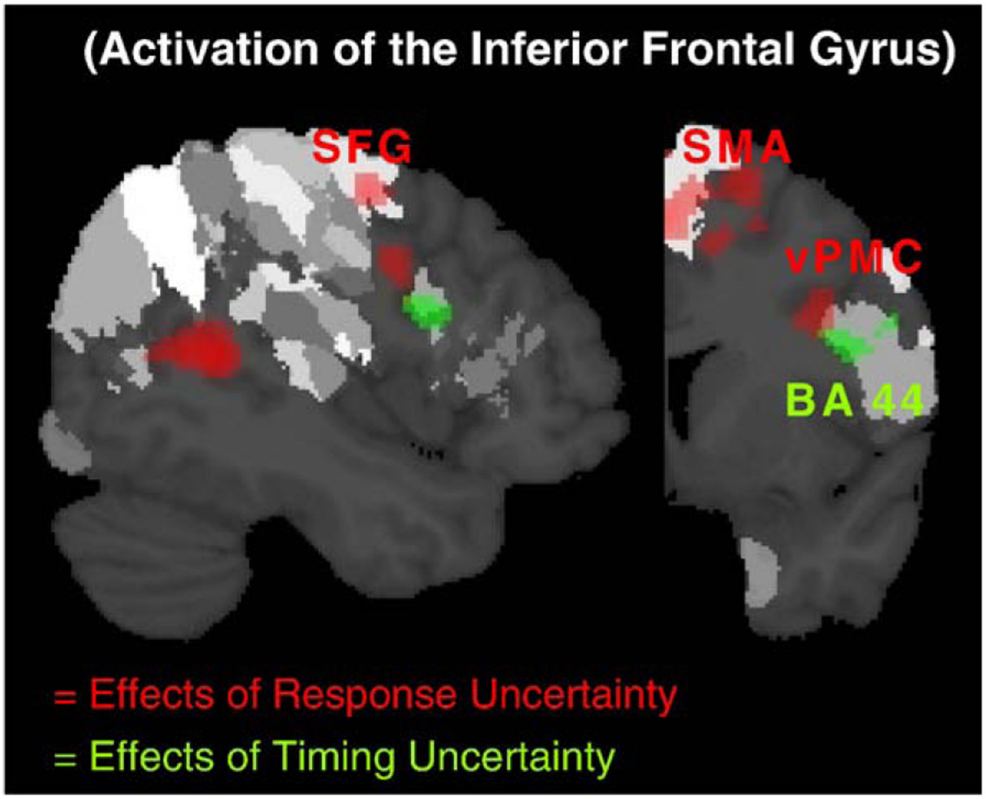

Fig. 5.

This picture illustrates the differential activation of frontal areas associated with the main effects of experimental factors (response type=red, timing uncertainty=green). Increasing uncertainty of movement direction activates the right ventral premotor cortex whereas increasing uncertainty of timing produces activation of a region into BA 44. These two activations are hence functionally and anatomically distinct from each other.

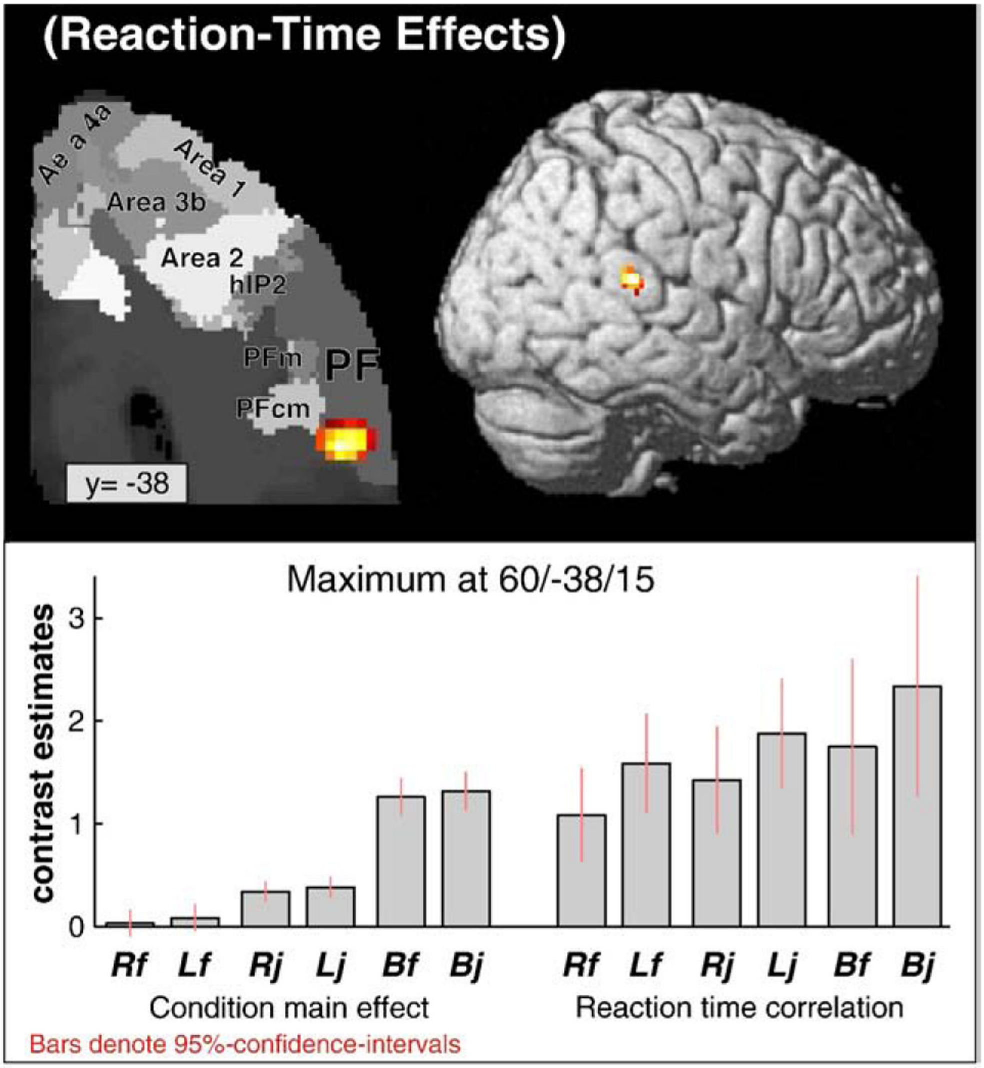

Fig. 6.

Testing for correlations between neuronal activity and reaction-time differences we observed activation in temporo-parietal Area PF (60/−38/15) overlapping with those found for increased uncertainty in movement direction and timing despite orthogonalising the covariate by condition. Increasing reaction times represent the behavioral indicator for processing speed and computational load. Considering the parietal activation pattern in the different contrasts and the behavioral data we propose that Area PF is mainly involved in updating movement plans in the predictive coding framework.