Dynamic Coding of Events within the Inferior Frontal Gyrus in a Probabilistic Selective Attention Task

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Abstract

■ Besides the fact that RTs in cognitive tasks are affected by the specific demands of a trial, the context in which this trial occurs codetermines the speed of the response. For instance, invalid spatial cues generally prolong RTs to targets in the location-cueing paradigm, whereas the magnitude of these RT costs additionally varies as a function of the preceding trial types so that RTs for invalid trials may be increased when preceded by valid rather than invalid trials. In the present fMRI study, we investigated trial sequence effects in a combined oddball and location-cueing paradigm. In particular, we tested whether RTs and neural activity to infrequent invalid or deviant targets varied as a function of the number of preceding valid standard trials. As expected, RTs in invalid and deviant trials were significantly slower when more valid standard trials had been presented beforehand. This behavioral effect was reflected in the neural activity of the right inferior/middle frontal gyrus where the amplitude of the hemodynamic response in invalid and deviant trials was positively related to the number of preceding valid standard trials. In contrast, decreased activity (i.e., a negative parametric modulation effect) was observed when more valid standard trials were successively presented. Further positive parametric effects for the number of preceding valid standard trials were observed in the left caudate nucleus and lingual gyrus. The data suggest that inferior frontal cortex extracts both event regularities and irregularities in event streams. ■

INTRODUCTION

Cognitive processes are often reflected in RT differences between experimental conditions of different cognitive demands. Usually, these effects are robustly observed when the RTs of all trials of each experimental condition are averaged. For example, in the location-cueing paradigm, subjects respond, on average, slower to target stimuli in trials with spatially invalid as compared to valid cues, reflecting the time needed to reorient attention in space (Posner, 1980). Typically, however, RTs are also characterized by trial-to-trial variations so that the magnitude of the "validity effect" in the location-cueing paradigm (RT invalid minus RT valid trials) varies from trial to trial.

Intertrial variability of RTs (or the validity effect, respectively) can, on the one hand, be attributed to unspecific factors such as, for example, vigilance fluctuations during the course of an experiment. On the other hand, there is also strong evidence for an influence of external factors such as, for instance, expectancy effects associated with the impact of trial sequence on the validity effect in the location-cueing paradigm (Jongen & Smulders, 2007). It has been shown that subjects extract and process regularities in stimulus streams even when they are instructed that these stimuli are presented randomly (Huettel, Mack, & McCarthy, 2002). Such a coding of stimulus sequence presumably subserves the generation of internal models of the sensory input, which are continuously updated and used to predict future stimulation according to Bayesian statistical theory (see, e.g., Friston, 2003, 2005).

In this framework, brain responses to infrequently occurring, unexpected, or deviant stimuli, for instance, the MMN and the P300 component of the EEG, have been considered to signal erroneous predictions (Friston, 2005) or the degree of surprise (Donchin, 1981). Likewise, the RT costs in response to invalidly cued targets in the location-cueing paradigm (i.e., the validity effect) may possibly reflect a prediction error signal in response to a violation of cue-induced expectancies. Such an error signal may accompany or even initiate processes related to spatial reorienting. Furthermore, it presumably alters the internal model by attenuating top–down expectancy. For instance, it has been shown that RT costs (RT invalid minus RT neutral trials) as well as benefits (RT neutral minus RT valid trials) are larger after a valid than after an invalid trial (Jongen & Smulders, 2007). This reflects a modulation of cue-induced expectancies which are attenuated after an expectancy violation and which are conversely enhanced after a correct prediction of the target location by the spatial cue. Interestingly, even preattentive measures, such as the MMN amplitude, covary with the number of preceding standard stimuli (Baldeweg, Klugman, Gruzelier, & Hirsch, 2004; Sams, Alho, & Näätänen, 1983), suggesting that the processing of sequences is an automatic ubiquitous process.

In the present study, we aimed at investigating trial sequence effects on RTs and neural activity in a combined

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location-cueing/oddball paradigm. For this reason, data from a previous fMRI study (Vossel, Weidner, Thiel, & Fink, 2009) were reanalyzed using parametric modulation methods. In this experiment, subjects were asked to make spatial frequency judgments of peripherally presented sinus gratings which were preceded by 80% valid cues and which were characterized by infrequent changes in color and orientation. These target feature changes (i.e., oddballs) were presented with the same frequency as the invalidly cued targets. Here, it was tested whether RTs as well as neural activation patterns in response to rarely occurring invalid trials (spatial domain) and color/orientation deviants (nonspatial domain) were affected by the number of preceding valid standard trials. We hypothesized that the RTs for change trials (i.e., invalid standard or valid deviant trials) would increase with the number of preceding valid standard trials (i.e., in change sequences). In contrast, we expected that RTs for validly cued standard targets would decrease with the number of repetitions of valid standard trials in which predictions are repeatedly confirmed (repetition sequences). In addition, we aimed at isolating those regions in the brain that signal confirmed or erroneous predictions by testing whether neural activity differentially covaried with the number of preceding valid standard trials for the two conditions (repetition vs. change sequences; see also Figure 1 for the hypothesized impact of trial sequence and experimental conditions). Based upon previous functional imaging work on the processing of predictable occurrences and event sequences, as well as of violations of the respective predicted outcomes (Huettel et al., 2002; Fletcher et al., 2001), we expected lateral prefrontal brain structures to respond to both event regularities and irregularities, that is, to show differential effects in the repetition and change sequences.

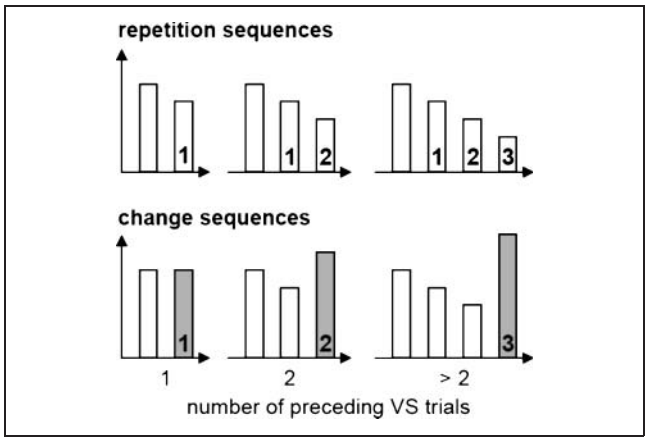

Figure 1. Hypotheses and methodological approach on the effects of trial sequence in the present study. In brain areas involved in the generation of predictive models, the repetition of validly cued standard target (VS) trials should be associated with constant or probably even reduced neural activity (upper row), as no updates to a putative internal model of sensory input are required. In contrast, in trial sequences involving a change of trial type (invalidly cued standard target or validly cued deviant target trials), neural activity should be enhanced as the number of preceding VS trials increases. The numbers on the bars depict the values which were entered in the design matrix as parametric modulators for the repetition and the change trials, respectively.

METHODS

Subjects

Initially, 24 subjects with no history of neurological or psychiatric disease gave written informed consent to participate in the original study (Vossel et al., 2009). Four participants were excluded from further analyses due to excessive head movement during fMRI scanning. In a first analysis, data from 10 subjects (5 men, 5 women; age range = 19–27 years; mean age = 23.9 years), for which at least five trials per experimental condition could be averaged, were analyzed (note that the experimental conditions were presented randomly with different trial sequences for the different subjects; see also below). Due to the arbitrary trial number cutoff, additional analyses were performed with 18 of the initial 20 subjects to test for the generality of the observed effects (for the remaining 2 subjects, some event sequences of interest never occurred during the experiment) (8 men, 10 women; age range = 19–38 years; mean age = 26.6 years). All subjects were right-handed as indexed by a handedness inventory (Oldfield, 1971). Intact color vision was tested with an adaptation of the Ishihara color tables (Velhagen & Broschmann, 2003).

Stimuli and Experimental Paradigm

The stimuli and the experimental paradigm are described in detail in Vossel et al. (2009). We used a location-cueing paradigm with central predictive cueing. Subjects were presented with two horizontally arranged boxes and a central diamond which served as a fixation point. Cues consisted of a 200-msec brightening of one side of the diamond depicting an arrowhead pointing to one of the peripheral boxes. The cue was followed by a target appearing for 100 msec in one of the boxes. To prevent temporal orienting, we used two randomly occurring cue–target intervals (400 and 700 msec). The cues were valid in 80% of the trials. The targets were circular sinusoidal gratings (0.9° eccentricity) with two different spatial frequencies ("fine" grating: 7 cycles per grating; "coarse" grating: 3 cycles per grating). Subjects were asked to report the spatial frequency of the target stimulus as quickly as possible by button presses with the index and middle fingers of their right hand. Fine and coarse gratings were presented randomly and with equal probability (i.e., 50%). The gratings could be either in grayscale or in red and green color, and were presented with four possible orientations (0°, 45°, 90°, 135°). One specific combination of color and orientation (e.g., grayscale grating with 0° orientation) was defined as the "standard target," which

was presented in 80% of the trials. Twenty percent of the targets, however, were "deviants," in which both the color and the orientation of the gratings changed (e.g., red–green gratings with 45°, 90°, and 135° orientation). Thus, a location-cueing paradigm was combined with a visual oddball paradigm, resulting in four experimental conditions (validly cued standard targets, VS; invalidly cued standard targets, IS; validly cued deviant targets, VD; invalidly cued deviant targets, ID). The experiment consisted of 959 trials, including 320 "null events" (Josephs & Henson, 1999) where a baseline stimulus was displayed, leading effectively to variable stimulus onset asynchronies (2000 msec, 4000 msec, 6000 msec, etc.).

Data Acquisition

T2*-weighted echo-planar (EPI) images with blood oxygen level dependent contrast (matrix size 64 × 64, voxel size 3.1 × 3.1 × 3.0 mm^3) were obtained using a 3-T MRI System (Trio; Siemens, Erlangen, Germany). Additional high-resolution anatomical images (voxel size 1 × 1 × 1 mm^3) were acquired using a standard T1-weighted 3-D MP-RAGE sequence. Nine hundred seventeen EPI volumes of thirty-six 3-mm-thick axial slices were acquired sequentially with a 0.3-mm gap (repetition time = 2.2 sec, echo time = 30 msec). The first 5 volumes were discarded to allow for T1 equilibration effects. The data were preprocessed and analyzed with Statistical Parametric Mapping software SPM5 (Wellcome Department of Imaging Neuroscience, London; Friston et al., 1995; www.fil.ion.ucl.ac.uk/spm5.html). To correct for interscan movement, the images were spatially realigned to the first of the remaining 912 volumes and, subsequently, re-realigned to the mean of all images after the first step. Then, the mean EPI image for each subject was computed and spatially normalized to the MNI single-subject template using the "unified segmentation" function in SPM5. 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 and to the T1 scan, which was coregistered to the mean of the realigned EPIs beforehand. All images were hereby transformed into standard stereotaxic space and resampled at 2 × 2 × 2 mm^3 voxel size. The normalized images were spatially smoothed using an 8-mm full-width half-maximum Gaussian kernel to meet the statistical requirements of the general linear model and to compensate for residual macroanatomical variations across subjects.

Statistical Analysis of Imaging Data

Data were analyzed with SPM5 employing a random effects model. For each VS, IS, and VD trial, the number of preceding VS trials (1, 2, and 3 or more VS trials; see Figure 1) was determined (separately for each subject).[1]

For the VS, IS, and VD regressors, a parametric regressor was defined at the single-subject level which coded for the number of preceding VS trials (1, 2, or >2). The remaining trials of each condition as well as the 25 invalidly cued deviant trials, trials with missed responses, catch trials, and the pauses of the experiment were added to the model as additional regressors. The event types were time-locked to the onset of the target by a canonical synthetic hemodynamic response function (HRF) and its first-order temporal derivative to account for temporal differences introduced by the order of slice acquisition. The six movement parameters of the realignment (rigid-body translation in the *x*-, *y*- and *z*-plane as well as rotation around the *x*-, *y*-, and *z*-axis) were included in the design matrix as additional regressors. Data were scan-wise globally scaled to reduce globally distributed confounding effects (Kiebel & Holmes, 2004) and high-pass filtered at 1/128 Hz.

For each subject, three contrast images were created which tested for the linear relationship between neural activity and the number of preceding VS trials in the three conditions (VS, IS, and VD). These contrast images were entered into a (1 × 3) second-level within-subjects ANOVA model. In the subsequent analyses, in which the trial number cutoff was discarded and data from 18 subjects were analyzed, the minimum trial number across conditions was included as a nuisance variable in the ANOVA to account for different data reliability across subjects. Inhomogeneity of variance and correlation of measurement were estimated with a Restricted Maximum Likelihood (ReML) algorithm. Significant positive or negative effects of the parametric modulators (i.e., linear relationships between the HRF amplitude and the number of preceding VS trials) of one or more experimental conditions were assessed with a nondirectional *F*-contrast ([1 0 0]; [0 1 0]; [0 0 1]). Results are reported at a significance level of $p < .005$ (uncorrected). Because cluster-level inference is only implemented for *t*-, but not for *F*-contrasts in SPM (Poline, Worsley, Evans, & Friston, 1997), we employed a cluster extent threshold of more than 100 contiguous voxels in order to minimize the chance of false-positive findings.

To illustrate the effects of the observed parametric modulators by means of the beta coefficients, we additionally performed a first-level analysis in which we separately modeled the VS, IS, and VD conditions with the different numbers of preceding VS trials (resulting in 3 × 3 = 9 conditions of interest). This allowed us to test for the effects of trial sequence and experimental condition in the voxels of interest with a 2 × 3 design. Here, the first two-level factor (condition: repetition vs. change) represented the effect of the mere repetition of VS trials in repetition sequences as compared to the trial sequences terminating with a change in stimulation. Because we expected equal effects for IS and VD change trials, the data of these conditions were pooled in the statistical analyses. The second factor

indicated the length of the trial sequences, and thus comprised three levels for either 1, 2, or >2 preceding VS trials. To avoid problems related to the violation of the sphericity assumption of univariate repeated measure ANOVAs with factors of more than two levels, we used multivariate analyses of variance (MANOVAs) (Vasey & Thayer, 1987) for testing the individual beta parameters (averaged beta parameters across submaxima) as well as for analyzing the RT data (see below). In addition to examining the main effects and the interaction, we also tested for linear trends of the repetition factor and its interaction. In the analyses without trial number cutoff, the minimal trial number across conditions was added as a nuisance variable. Results are reported at a significance level of $p < .05$.

Statistical Analysis of Behavioral Data

RTs faster than 100 msec (i.e., anticipated responses) were excluded from the analysis. Median RTs were separately calculated for the different conditions (VS, IS, and VD trials preceded by 1, 2, or >2 VS trials) at the single-subject level. RTs for IS and VD trials were pooled to test for the effects of change versus repetition sequences. Thus, as for the analyses of the beta-parameters of the fMRI data, the effects of trial history and experimental condition were assessed according to a 2 (condition: change vs. repetition sequences) × 3 (1, 2, or >2 preceding VS trials) design. A MANOVA was employed and linear trends for the repetition factor were tested in case of significant main effects or a significant interaction effect. In the analyses without trial number cutoff, the minimal trial number across conditions was added as a nuisance variable. Results are reported at a significance level of $p < .05$.

Comparison of Activation Foci in Right Frontal Cortex across Different Studies

To relate the observed activation in the right inferior and middle frontal gyrus (see Results section) to the results of prior studies on the processing of deviant or unexpected information, we listed the peak voxel coordinates within right frontal cortex of prior studies employing probabilistic location-cueing paradigms, oddball or novelty oddball paradigms, tasks that investigate the processing of surprise and uncertainty (i.e., probabilistic context), as well as neural correlates of the MMN. Where necessary, the *x*-, *y*-, and *z*-coordinates were transformed from Talairach into MNI space with the help of the function tal2mni.m (http://imaging.mrc-cbu.cam.ac.uk/downloads/MNI2tal/tal2mni.m). We superimposed those activation peaks that were located within a distance of ±10 mm from the maxima observed in the present study (see Table 1) on a T1-weighted template brain using MRIcro software (www.sph.sc.edu/comd/rorden/mricro.html) (see Figure 5).

RESULTS

Behavioral Data

The effects of trial sequence in the different experimental conditions are depicted in Figure 2.

A 2 (condition: change vs. repetition sequence) × 3 (1, 2, or >2 preceding VS trials) MANOVA yielded a significant main effect of condition [$F(1, 9) = 84.01, p < .001$], reflecting overall faster responses in the repetition (i.e., VS) than in the change (i.e., IS and VD) trials. Moreover, we observed a significant main effect of repetition [$F(2, 8) = 5.78, p < .05$] as well as a significant interaction effect [$F(2, 8) = 9.95, p < .01$]. Significant linear trends were observed for these latter terms of the MANOVA [number of prior VS trials: $F(1, 9) = 12.67, p < .01$; Condition × Number of prior VS trials interaction: $F(1, 9) = 15.05, p < .01$]. These results indicate a differential prolongation of RTs in change (see Figure 2B) as compared to repetition sequences (see Figure 2A) with an increasing number of preceding VS trials. In other words, the RT costs in response to invalidly cued or deviant targets were increased when more VS trials had preceded these trials. The condition main effect, the Condition × Number of prior VS trials interaction, and its linear trend were also observed in the analysis with 18 subjects [main effect of condition: $F(1, 16) = 5.32, p < .05$; interaction: $F(2, 15) = 5.43, p < .05$; linear trend of the interaction: $F(1, 16) = 11.37, p < .01$]. The main effect of the number of VS repetitions did not reach significance.

Neural Data

The *F* test on the parametric regressors of the three conditions revealed three areas in which significant linear

Table 1. fMRI Data

	MNI Coordinates				
Region	*x*	*y*	*z*	*F Score*	*p*
Right Inferior & Middle Frontal Gyrus (126 Voxels)					
Inferior frontal gyrus/ operculum	50	20	39	9.15	<.001
	36	14	35	8.31	<.001
Middle frontal gyrus	46	14	35	6.16	<.002
Left Caudate Nucleus (131 Voxels)					
Caudate nucleus	−14	−2	19	11.05	<.001
	−6	4	7	9.98	<.001
Left Lingual and Fusiform Gyrus (189 Voxels)					
Lingual gyrus	−18	−78	−13	11.52	<.001
Fusiform gyrus	−28	−78	−15	11.63	<.001

Results of the *F*-contrast testing for a linear effect of the number of preceding valid standard trials in one or more experimental conditions (VS, IS, and VD).

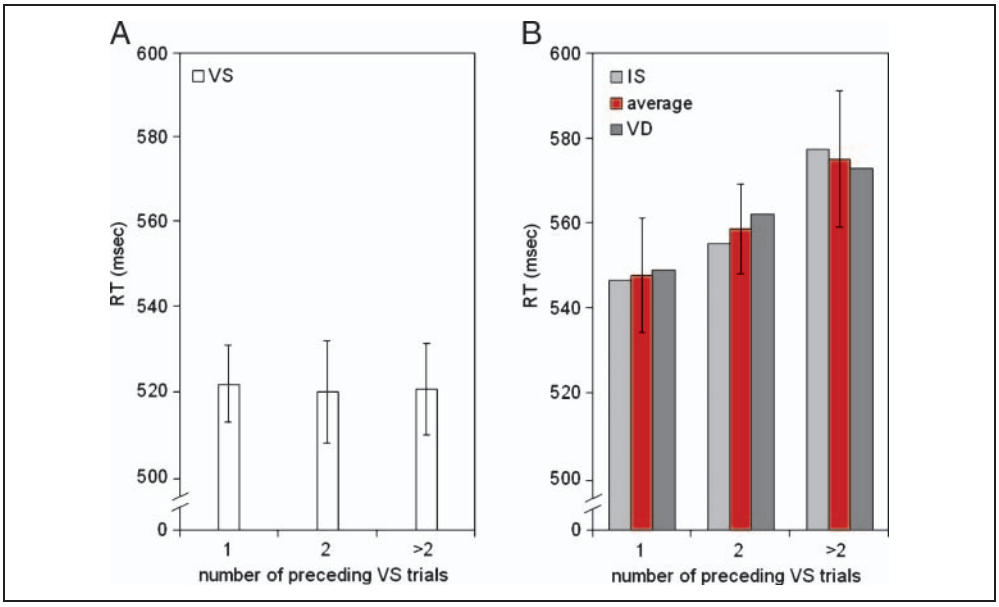

Figure 2. Effects of trial sequence on RTs in the different experimental conditions. Mean of the individual median RTs and standard errors of the mean (*SEM*) as a function of experimental condition [repetition sequences (A) vs. change sequences (B)] and number of preceding VS trials.

relationships with the number of preceding VS trials occurred (see Table 1).

For the cluster within the right inferior and middle frontal gyrus, the MANOVA on the averaged beta parameters revealed neither a significant main effect of condition [$F(1, 9) = 4.48, p = .063$] nor a significant main effect of the number of preceding VS trials [$F(2, 8) = 3.87, p = .067$], but a significant Condition × Number of preceding VS trials interaction effect [$F(2, 8) = 40.18, p < .001$]. The test for linear trends for the Condition × Number of preceding VS trials interaction effect was significant [$F(1, 9) = 43.11, p < .001$], reflecting increasing activity with the number of preceding VS trials in the change sequences (IS and VD), but not in the repetition sequence (i.e., in VS trials) (see Figure 3).

In the left caudate nucleus (see Figure 4A), we observed both a significant main effect of the number of preceding VS trials [$F(2, 8) = 13.79, p < .01$] and a significant interaction effect [$F(2, 8) = 5.73, p < .05$]. There was no significant main effect of condition [$F(1, 9) = 1.7, p = .225$]. Linear trends were observed for the number of VS trials main effect [$F(1, 9) = 28.19, p < .001$] and the interaction effect [$F(1, 9) = 12.87, p < .01$]. For the left lingual and fusiform gyrus (see Figure 4B), both main effects were significant [condition: $F(1, 9) = 14.57, p < .01$; number of prior VS trials: $F(2, 8) = 13.07, p < .01$]. However, there was no significant interaction effect [$F(2, 8) = 1.82, p = .224$]. A linear trend was present for the number of preceding VS trials [$F(1, 9) = 24.32, p < .01$].

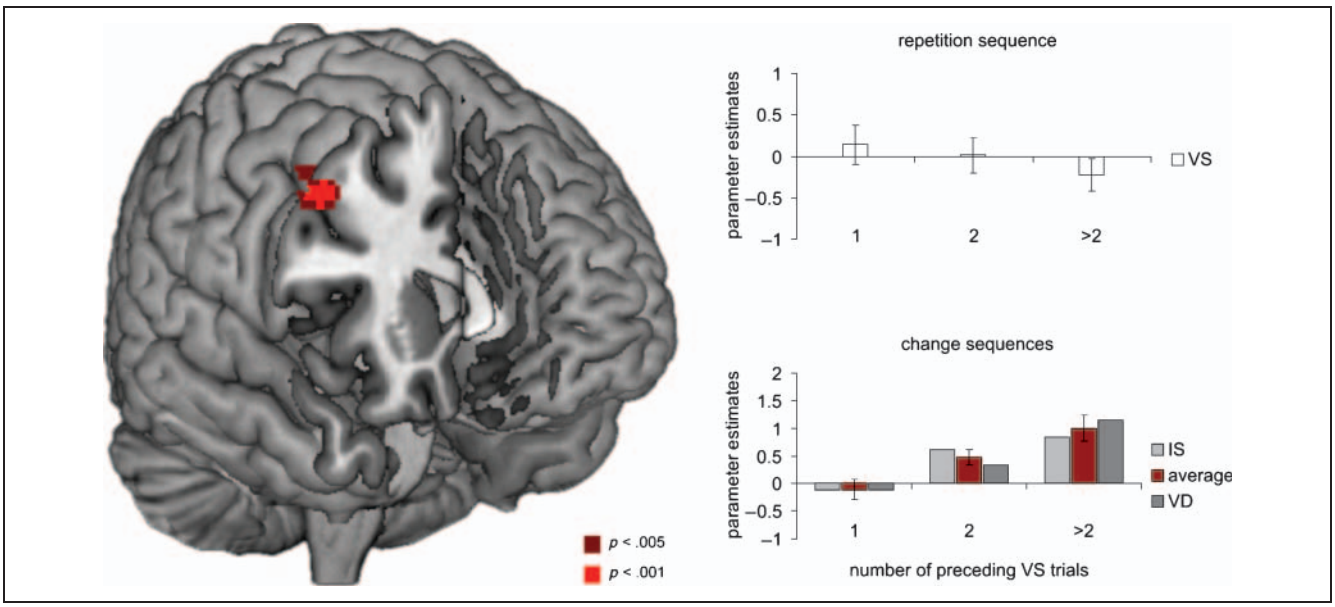

Figure 3. Differential parametric responses for repetition (VS) (top right) and change (IS, VD) sequences in the right inferior and middle frontal gyrus. The activation is depicted on the T1 template image provided by MRIcroN (www.sph.sc.edu/comd/rorden/mricron/).

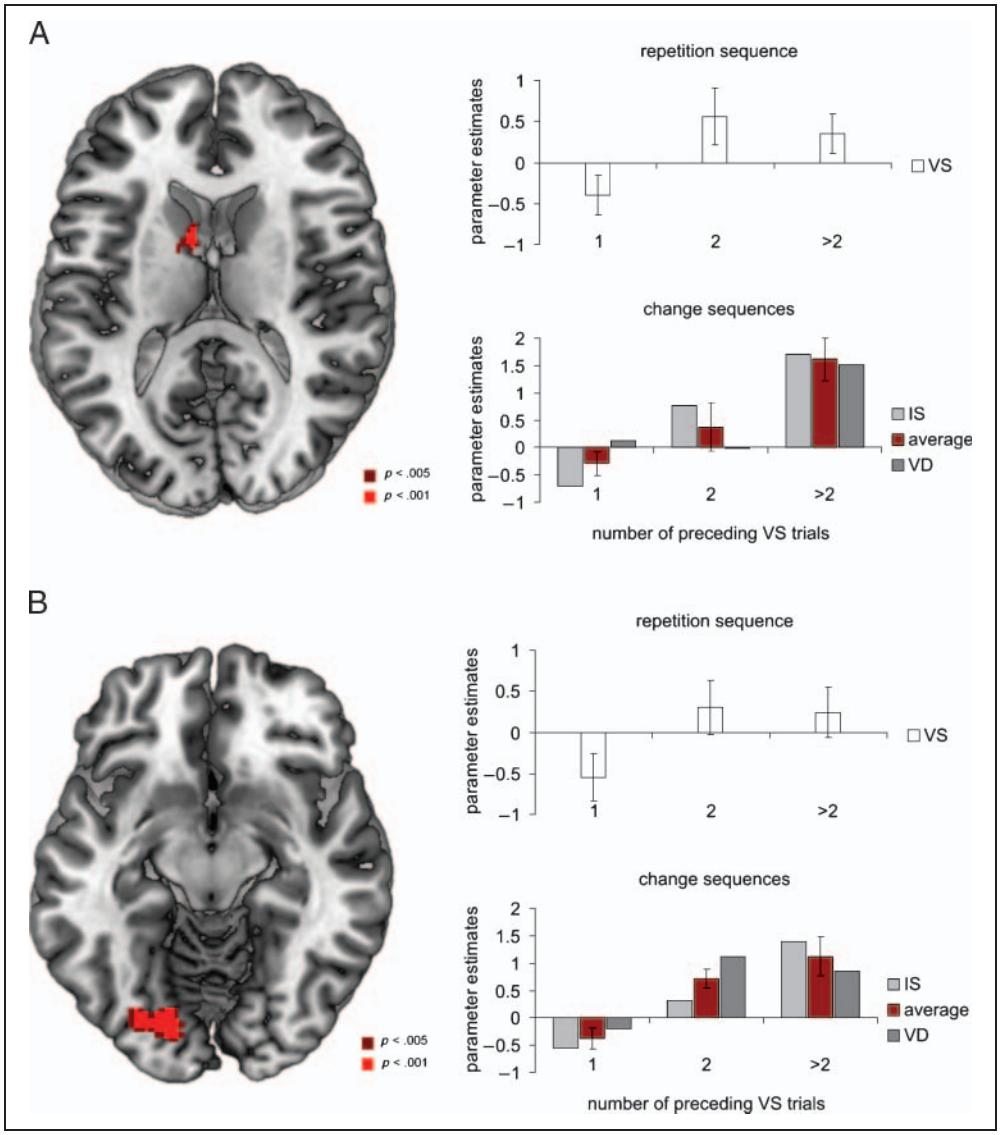

Figure 4. Parametric responses in the left caudate nucleus (A) and lingual gyrus (B) for repetition and change sequences.

The analyses without trial number cutoff with all 18 subjects confirmed the differential trial sequence effect within the right inferior and middle frontal gyrus [global F-contrast: 100 voxel, submaxima at $x = 48, y = 30, z = 33, F = 9.91$, $p < .001; x = 44, y = 38, z = 31, F = 5.83, p < .002$). Here, a significant Condition × Number of prior VS trials interaction effect was observed [$F(2, 15) = 18.18, p < .001$], as well as a significant linear trend of this interaction [$F(1, 16) = 38.50, p < .001$], with decreasing neural activity with successive VS repetitions and increasing activity in change sequences. No other region showed significant parametric effects. Also, the left caudate nucleus and left lingual and fusiform gyrus did not show significant activation in this analysis.

DISCUSSION

In the present study, we investigated the processing of infrequently occurring deviant stimuli (location or color/orientation changes) as a function of the number of preceding standard trials. In particular, we contrasted trial sequences in which VS trials were successively repeated with sequences that involved a change in trial type. We observed that RTs for both IS as well as for VD targets increased with the number of preceding standard trials. The fMRI data revealed that neural activity in the right inferior and middle frontal gyrus increased in IS and VD trials when more VS trials had preceded these trials. In contrast, a negative trend (decreased activity) was observed for sequences in which VS trials were presented in succession. Further parametric modulation effects for the number of preceding VS trials were observed in the left caudate nucleus and the left lingual and fusiform gyrus. The results can be best explained along the lines of recent theories on probabilistic perceptual inference (Friston, 2005). The data suggest that right inferior frontal cortex particularly responds to unexpected events, in line with prior studies reporting activation in right inferior and middle frontal cortex in response to infrequently occurring or odd stimuli in probabilistic location-cueing, oddball, stimulus sequence, and MMN paradigms.

Processing of Event Irregularities

The behavioral data in the present analysis consistently revealed slower RTs for invalidly cued targets as well as for unexpected changes in the color and orientation of the target stimulus (see also Vossel et al., 2009). However, the magnitude of the RT costs depended on the sequence in which the IS or VD trials occurred, so that relatively slower RTs were observed for sequences with more preceding VS trials. Thus, the data suggest that the RT costs in these conditions were a compound of two different underlying processes. First, we suppose that the cognitive process which was provoked by the respective trial type per se led to a prolongation of the response. Thus, visuospatial attention had to be reoriented to the opposite side of the display to process and discriminate the target stimulus in invalid trials, whereas the color and orientation changes in deviant trials distracted the subjects and demanded a refocusing on the relevant stimulus features (i.e., the spatial frequency of the target). These sources of RT costs are presumably independent of the context in which a trial occurs. On top of that, however, the RT costs comprised a trial-sequence-dependent component, supposedly reflecting the effect of the unexpectedness of the change in stimuli or the amount of reconfiguration demand. In line with this, studies employing the information theoretic concepts of entropy and surprise in order to formally quantify the predictability and unexpectedness of events in cueing or sequential reaction time tasks have shown that RTs as well as neural responses covary with these measures (Harrison, Duggins, & Friston, 2006; Strange, Duggins, Penny, Dolan, & Friston, 2005). For instance, for the probabilistic cueing of motor responses, such models that incorporate entropy and surprise explain RT data and measures of corticospinal excitability better than the categorical model in which only the effects of invalid and valid cueing are compared (Bestmann et al., 2008). Similarly, the P300 amplitude has been shown to vary with the amount of surprise that is associated with an event (Mars et al., 2008). Moreover, the degree of surprise has been related to the activity in thalamic and visual areas as well as in a fronto-parietal network including inferior frontal cortex (Strange et al., 2005).

Interestingly, trial sequence effects have been reported for a variety of tasks ranging from modulations of RTs and neural activity by the preceding trial in higher cognitive tasks (Jongen & Smulders, 2007; Huettel et al., 2002; Weidner, Pollmann, Müller, & von Cramon, 2002; Pollmann, Weidner, Müller, & von Cramon, 2000; see also Fecteau & Munoz, 2003 for a review) to the modulation of preattentive measures such as the MMN component (Baldeweg et al., 2004; Sams et al., 1983). This implies that event sequences are automatically and implicitly processed. This notion is also corroborated by the study of Huettel et al. (2002), which showed that stimulus sequence patterns affect RTs when the subjects are told that the stimulus presentation is purely randomized. The same was true for the present study in which the trial sequences of interest occurred at random. It has to be noted, however, that in our study, subjects were informed about the overall frequency of VS, IS, and VD trials. It could be speculated that this contextual information may affect the degree to which predictive codes are extracted from past information, that is, that the effects of trial sequence are probably attenuated as the ratio of valid to invalid or standard to deviant trials decreases. In line with this note of caution, it has recently been shown that neural repetition suppression (i.e., the decrease in the neural response to a specific stimulus with repeated presentation) is affected by the probability of the repetitions (Summerfield, Trittschuh, Monti, Mesulam, & Egner, 2008). Because repetition suppression to face stimuli in the fusiform face area was more pronounced in blocks where stimulus repetitions were likely to occur, the authors concluded that the repetition suppression phenomenon reflects the reduction of prediction error when an event is expected. Interestingly, however, repetition suppression was still observed when stimulus repetitions were very unlikely. Taken together, these findings—in combination with the fact that we observed significant trial sequence effects in the present study despite our subjects knowing that the cue could be invalid and that the target's color and orientation would change in a proportion of the trials—support the idea that predictive perceptual inference is a generic automatic process which assumes that the stimulation is usually consistent across short time scales. The degree to which the resulting predictive codes are implemented to adjust the system for upcoming stimulation, however, presumably depends on the overall "top–down" informed context in which an event occurs.

Our results furthermore demonstrate that this coding is not restricted to the mere physical properties of a particular stimulation or to a required motor response. In the present study, both the physical location (left or right), the spatial frequency of the target stimulus (fine or coarse grating), and the associated motor response (index or middle finger) randomly changed from trial to trial within all of the investigated trial sequences. In particular, the results for the IS condition show that the coding can occur for abstract stimulus–stimulus (i.e., cue–target) relationships.

It has to be noted that unlike neural activity in inferior frontal cortex (see below), the RTs were not reduced in the repetition sequences when VS trials were successively repeated. This could, on the one hand, reflect a ceiling effect in that the trial-type repetition could not decrease the RTs over and above the speeding introduced by prior knowledge of the target position. On the other hand, it has been observed that stimulus repetition effects are stronger when exactly the same physical stimulus is successively repeated than when alternating sequences are presented, in which stimulus features change from trial to trial (i.e., in AAAA sequences as opposed to ABAB sequences; Huettel et al., 2002). Whereas both sequences were accompanied by slower responses in case of sequence violations in the

latter study, only the repeating sequences elicited faster responses with repeated presentation of the stimuli (Huettel et al., 2002). Because our trial sequences were as well characterized by changes in physical stimulus features such as position and spatial frequency, one could speculate that these alternations prevented (or maybe even masked) an RT acceleration.

Neural Representation of the Extraction of Event Irregularities

What brain areas are involved in the extraction of event regularities and in the brain response to irregular events? In the present study, the inferior and middle frontal gyrus of the right hemisphere exhibited the most clear-cut differential response to repetition as compared to change sequences. In this region, the neural response to a trial change was positively related to the number of preceding VS trials, whereas there was a negative relationship for the repetition sequences. In accordance with this pattern, this region has been shown to be activated in many different paradigms in which the least common denominator is the occurrence of unexpected events or sudden changes in stimulation (see Figure 5). Out of 25 considered studies, 18 reported activation maxima close to the region showing the differential trial sequence effect in the current study. When the distance threshold was lowered to ±15 mm, this number increased to 21 out of 25 studies. The activation observed in the present study was anatomically close to those regions that have been shown to respond to violations of implicitly processed stimulus sequences or learned associations (Huettel et al., 2002; Fletcher et al., 2001). This area is also commonly observed to be activated when invalid and valid trials are contrasted in the location-cueing paradigm and when the response to deviant or novel stimuli in oddball paradigms is investigated (see Figure 5). A study on the neural correlates of the MMN also observed activation of right inferior frontal cortex. These findings from imaging studies converge with evidence from studies in patients with lesions in prefrontal cortex. For instance, damage to prefrontal areas disrupts the generation of brain signals of stimulus novelty, such as the novelty P300 (Daffner et al., 2000), and a recent study moreover suggests that prefrontal lesions impede the ability to process the temporal contingency (i.e., the predictive relationship) between novel and target stimuli (Barcelo & Knight, 2007).

The region in the inferior and middle frontal gyrus showing the differential trial sequence effect in the present analysis was located within the same area that showed a significant conjunction effect in our previous data analysis (Vossel et al., 2009). Hence, this region showed both enhanced activity for invalid as compared to valid as well as for deviant as opposed to standard trials in the latter study, further corroborating a general role of this region for change detection. Interestingly, the second region revealed by this conjunction, the intraparietal sulcus, did not show a trial sequence effect in the present analyses. This may suggest that there is a hierarchical relationship between frontal and parietal areas in that frontal regions process contextual information (e.g., like trial history) and, accordingly, initiate the required responses in parietal areas (reorienting of attention or distractor inhibition). This would imply that frontal areas mediate the trial-sequence-dependent component in RTs, whereas parietal regions mediate the context-independent cognitive processes evoked by the trial type per se (see discussion of the behavioral data in the Processing of Event Irregularities section). Indeed, there is evidence that, in task preparation paradigms, the activity in lateral prefrontal cortex activity precedes the activity in intraparietal cortex (Brass, Ullsperger, Knoesche, von Cramon, & Phillips, 2005).

The question whether left- and right-hemispheric frontal brain structures are differentially involved in the processes outlined above is still a matter of debate. Although the latter patient study showed that certain ERP components are disrupted for novel stimuli in the hemifield contralateral to prefrontal damage only, other ERP components are

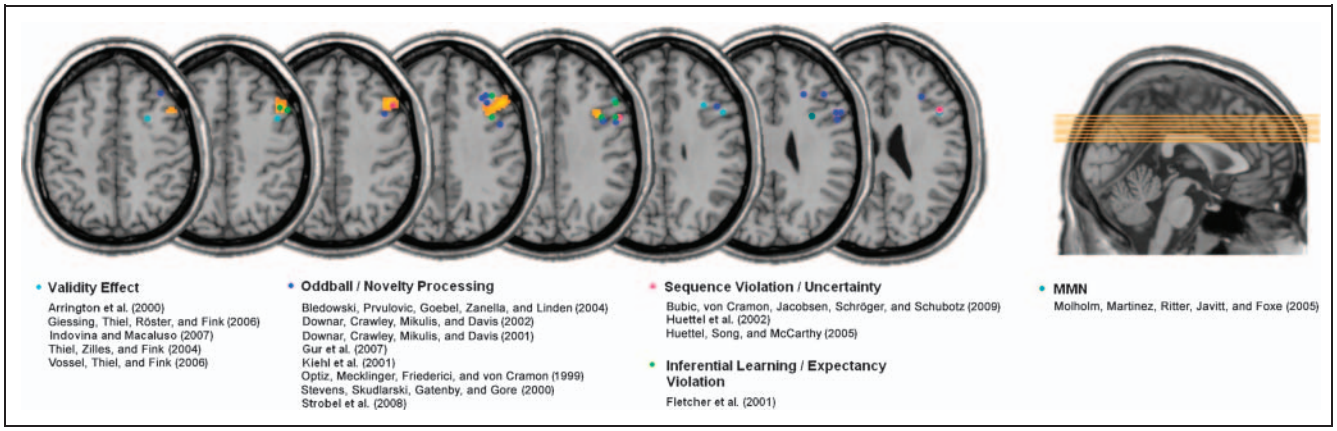

Figure 5. Overview over studies reporting activation within the IFG/MFG complex of the right hemisphere in response to unexpected, deviant, or novel stimuli.

bilaterally affected (Barcelo & Knight, 2007). There is, so far, no clear evidence for a differential impairment of left- versus right-hemispheric patients in the processing of centrally presented novel stimuli (Daffner et al., 2000). Neuroimaging studies in healthy subjects mainly report either right-hemispheric or bilateral frontal activation in response to unexpected or deviant stimuli. A study that directly compared the amplitude of the hemodynamic response for voxels of the left and right hemisphere in a three-stimulus oddball paradigm in 100 volunteers observed greater hemodynamic activity in prefrontal structures of the right hemisphere for both novel and target stimuli (Stevens, Calhoun, & Kiehl, 2005). In the present study, only the right inferior and middle frontal gyrus exhibited the expected diametric response pattern with decreased and increased activity for the two event sequences. Likewise, right-lateralized differential effects for the learning of associations on the one hand and for the processing of unpredicted outcomes on the other hand have been reported by Fletcher et al. (2001).

Moreover, it has been proposed that (although bilateral prefrontal areas are more generally involved in various forms of executive functions) the right IFG particularly mediates inhibitory control such as implicated in response inhibition, task-set switching, as well as interference from long-term or working memory or from previous trials (see Aron, Robbins, & Poldrack, 2004, for a review). Hence, our differential trial sequence effect in the inferior frontal gyrus could likewise reflect an interruption signal of the ongoing target detection and discrimination process in VS trials accompanied by an inhibition of premature responses until reorientation is accomplished in IS trials (see also Arrington, Carr, Mayer, & Rao, 2000, for a similar interpretation of inferior frontal activity in invalid trials) or until the relevant stimulus features (spatial frequency) are identified among distracting features of the target stimulus in the VD trials. Alternatively, the inferior frontal gyrus response in the present study could relate to the amount of reconfiguration that presumably accompanies change trials. Reconfiguration is required in a trial that is dissimilar to the previous one, and our data suggest that this effect is, moreover, modulated by the prior repetition of similar trials.

In the analyses with a predefined trial number cutoff of more than five trials per condition, two other brain regions (i.e., the left caudate nucleus and the left lingual and fusiform gyrus) showed significant parametric trial sequence effects. These regions could not be replicated in the analysis of all 18 subjects, probably due to a lack of power caused by insufficient sampling of the HRF in case of small trial numbers per condition. Alternatively, these regions showed false-positive activation in the first analysis. However, it has previously been observed that the caudate nucleus responds to novels or targets in oddball tasks as well as to violations of stimulus sequence patterns (Strobel et al., 2008; Melcher & Gruber, 2006; Huettel et al., 2002; Kiehl, Laurens, Duty, Forster, & Liddle, 2001). In the left lingual and fusiform gyrus, activity was possibly enhanced by top–down mechanisms due to an increasing expectation of valid trials in the VS (repetition) sequences, which required more effort (i.e., higher neural activity) when the trial type changed. Alternatively, it could be speculated that the response pattern in visual cortex in the present study was related to (trial sequence) transition effects (Jack, Shulman, Snyder, McAvoy, & Corbetta, 2006; Fox, Snyder, Barch, Gusnard, & Raichle, 2005; Shulman et al., 2003; Konishi, Donaldson, & Buckner, 2001), which are stronger for longer sequences (number of prior VS trials main effect) as well as for sequences terminating with a change in trial type (condition main effect).

Taken together, although all three regions identified to vary as a function of trial sequence in the present study (inferior frontal cortex, caudate nucleus, lingual gyrus) likewise responded to unexpected changes in stimulation (*change sequences*), the response pattern in visual cortex as well as in the caudate nucleus in the *repetition sequences* was less clear and less reliable than for the inferior frontal region where we observed a decrease in activity with more VS repetitions. In other words, although inferior frontal cortex responded both to confirmed and violated expectancies in an opposed manner, the caudate region and extrastriate cortex rather responded to violations of the expected input only.

Conclusion

In sum, our data show that in paradigms with infrequently occurring stimulation, RTs are affected by trial sequence. This effect is mediated specifically by the activity of parts of the inferior and middle frontal gyri, which are involved in the extraction of event regularities and, accordingly, in signaling confirmed and erroneous expectations or the amount of reconfiguration that is triggered by dissimilar successive trials, respectively.

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Note

1. The trial numbers for the different experimental conditions preceded by 1, 2 or >2 VS trials in all 18 subjects ranged from 85 to 103 (mean = 93.4, *SD* = 4.8), 30 to 45 (mean = 38.7, *SD* = 4.0), 16 to 44 (mean = 28.3, *SD* = 7.2) for the VS, 14 to 31 (mean = 24.9, *SD* = 4.9), 6 to 13 (mean = 8.7, *SD* = 2.1), 3 to 10 (mean = 6.4, *SD* = 1.9) for the IS and 14 to 32 (mean = 23.1, *SD* = 5.2), 4 to 15 (mean = 8.8, *SD* = 2.7), 3 to 15 (mean = 7.2, *SD* = 3.2) for the VD trials, respectively.

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