Temporally Remote Destabilization of Prediction After Rare Breaches of Expectancy

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Abstract: While neural signatures of breaches of expectancy and their immediate effects have been investigated, thus far, temporally more remote effects have been neglected. The present fMRI study explored neural correlates of temporally remote destabilization of prediction following rare breaches of expectancy with a mean delay of 14 s. We hypothesized temporally remote destabilization to be reflected either in an attenuation of areas related to long-term memory or in an increase of lateral fronto-parietal loops related to the encoding of new stimuli. Monitoring a deterministic 24-digit sequence, subjects were asked to indicate occasional sequential omissions by key press. Temporally remote destabilization of prediction was expected to be revealed by contrasting sequential events whose equivalent was omitted in the preceding sequential run n-1 (destabilized events) with sequential events without such history (nondestabilized events). Temporally remote destabilization of prediction was reflected in an attenuation of activity in the dorsal frontomedian cortex (Brodmann Area (BA) 9) bilaterally. Moreover, activation of the left medial BA 9 was enhanced by contrasting nondestabilized events with breaches. The decrease of dorsal frontomedian activation in the case of destabilized events might be interpreted as a top-down modulation on perception causing a less expectation-restricted encoding of the current stimulus and hence enabling the adaptation of expectation and prediction in the long run. *Hum Brain Mapp 00:000–000, 2011.* © 2011 Wiley-Liss, Inc.

Key words: sequential event structure; dorsal frontomedian cortex; long-term memory; adaptation of prediction; top-down control

INTRODUCTION

We can adapt our expectations, even when they are deeply rooted in our experience. When a particular breach of expectancy constantly recurs in the context of highly familiar events, e.g., in music or daily routines, it will challenge our expectations and trigger their adaptation in the long run. However, event prediction is realized in a noisy system and environment. Computationally, it might best be described as a Bayesian strategy, optimizing expectation by weighted combinations of priors and sensory likelihoods [Körding and Wolpert, 2006]. Accordingly, as long as they occur in an unpredictable fashion, rare breaches of expectancy should not cause sustained changes of what has been referred to as our internal models [Grush, 2004; Miall and Wolpert, 1996; Schubotz, 2007; Wolpert and Kawato, 1998]. The system has to achieve an effective balance between maintaining successful internal models on the one hand and adapting internal models to persistently altered environmental conditions on the other hand.

However, while the neural signatures of detecting unexpected events and those of immediate regulatory mechanisms, such as the evaluation of such deviants or the reprocessing of maintained information, has been addressed

in various respects in cognitive neuroscience, including the domains of language processing [Friederici, 2004; Grodzinsky and Friederici, 2006] and visual [Corbetta and Shulman, 2002] and auditory attention [Friedman et al., 2001; Winkler et al., 2009], we are largely ignorant about temporally more remote manifestations of unexpected events.

This study used fMRI to investigate the neural signatures of temporally remote effects inherited by preceding breaches of expectancy. Subjects were required to monitor a deterministically repetitive 24-digit sequence that they had learned before entering the fMRI session. Rare, unpredictable breaches of expectancy were induced by omissions of one digit or several consecutive digits without leaving a temporal gap. Subjects were asked to immediately indicate these omissions via key press. We compared expected events (sequence-congruent events) that were preceded by a breach in the preceding sequential run (n-1) with expected events that had no such history. In the following, the former will be referred to as destabilized events, the latter as nondestabilized events. Neural correlates of these two categories of expected events were hypothesized to differ in that in the case of destabilized events, preceding breaches weaken the internal model and prediction becomes temporarily ambiguous when the same part of the sequence recurs. Because of the length of the sequence and the amount of omitted digits, the mean delay between destabilized events and preceding breaches was 14.16 ± 2.49 s.

By comparing destabilized events to nondestabilized events we tested the following two hypotheses. Firstly, temporally remote destabilization could be reflected in a reduction of activity in areas retrieving sequential knowledge from long-term memory, i.e., an attenuation of top-down control in favor of a less expectation-restricted perception. Candidate areas were the hippocampus or the parahippocampal gyrus [Eichenbaum and Fortin, 2009; Fortin et al., 2002; Wallenstein et al., 1998] and rostral prefrontal areas attributed to higher-level mnemonic control [Simons and Spiers, 2003]. Second, temporally remote destabilization could be reflected in an increase of activity in areas related to the encoding of the current expected stimulus, as recurrence of the previous deviant stimulus might be expected. In the latter case, activation in lateral fronto-parietal networks would be observed that should be akin to the activation pattern during the breach itself [Bubic et al., 2009; O'Connor et al., 2010].

METHODS

Participants

Data of 20 right-handed (mean Oldfield score 80, range 53–100) healthy volunteers (7 female, mean age 24.7 years, standard deviation (SD) = 2.0, range, 22–29) were analyzed for the study. Data of four additional subjects were excluded from analysis because of their low breach detection rate. They were informed about potential risks of MRI, screened by a physician and all of them gave informed consent before participating and received a financial compensation for their participation. The experimental standards were according to the Declaration of Helsinki approved by the local ethics committee (Medical Faculty, University of Cologne).

Stimuli and Task

Stimuli were black and red digits (numbers 1–8) that were presented in the centre of the monitor with a visual angle smaller than 1° in height and width. Digits formed a 24-digit sequence (e.g., 123 123 765 765 234 234 876 876) that was hierarchically structured by ascending and descending repeated triplets. This stimulus-given triplet-pattern results in the same chunking for all participants and caused fast learning of the sequence. In order to avoid effects of digit magnitude, the run direction and triplet positions were both counterbalanced across subjects by employing altogether four sequences: 123 123 765 765 234 234 876 876, 765 765 123 123 876 876 234 234, 321 321 567 567 432 432 678 678, 567 567 321 321 678 678 432 432.

The digit sequence was presented isochronously digit by digit, each for 500 ms with an inter-stimulus-interval of 200 ms. The entire sequence was presented cyclically without temporal gaps between the end of one and the start of the following sequence. Unpredictably, 1, 3, 6, or 12 digits were omitted at positions at which the first-after-omission position was a chunk boundary, i.e. the first position of a triplet. Importantly, omissions were not related to the experience of a temporal gap, i.e. in case of omissions digits were presented isochronously, too. Episodes of different lengths were omitted as we were additionally interested in whether the strength of breaches of expectancy elicits activation in the lateral fronto-parietal network to different extents. Results of this parametric manipulation of breaches of expectancy will be reported elsewhere.

Participants performed two tasks concurrently. Manual responses were made with one response key. In the omission detection task participants were required to respond as fast as possible by pressing the key whenever they detected a sequential omission, whereas in the color detection task participants were asked to press the key when digits were presented in red (about 1.3% of all digits) instead of the otherwise black presentation color. Note that the color detection task was implemented to investigate the main effect of breaches that will be reported elsewhere, together with the parametric effect of the omission size on breach detection.

During the experiment 4,077 digits were presented (54 in red, 4,023 in black). Twenty pauses of 7 s were inserted across the session as resting baseline (R). The correct sequence was presented without sequential omissions 80 times (42% of all sequences). 148 omissions, i.e. breaches of expectancy (B), were inserted randomly in the remaining sequences. Thereby one sequence could be disrupted

by more than one omission. In order to investigate the research question on the effect of temporally remote destabilization of prediction reported here, 54 expected events were randomly determined, half of them serving as destabilized events (DE) and half of them as nondestabilized events (NDE). The effect of temporally remote destabilization was expected to be observed when sequential positions of omissions in the sequence *n*-1 were repeatedly reached in the sequence *n*. We analyzed expected events as brain signatures of temporally remote destabilization of prediction were expected to be observed in the absence of a present breach, i.e., when participants' response was not required. For a better understanding of destabilized events an example is given in the following. The omission (*) of the second 765 (123 123 765 *** 234 234 876 876) could be noticed by participants when the 2 bold and underlined was presented instead of the expected 7. In this example, the proposed effect of temporally remote destabilization of prediction is expected in the subsequent sequence at the 7 of the second 765 (123 123 765 765 234 234 876 876). In contrast to destabilized events, nondestabilized events were positioned such that they did not have the history of an omission in the previous sequential run. At the same time, it was controlled for the sequential position of the two categories of expected events, as well as for the mean distance between omissions and destabilized events on the one hand and omissions and nondestabilized events on the other hand. Thereby, the mean distance between expected digits and preceding omissions was 14.16 s [standard deviation (SD) = 2.49] in case of destabilized events and 14.23 s (SD = 6.5) in case of nondestabilized events. In order to control for the mean distance, the SD in case of nondestabilized events had to be larger than that in case of destabilized events, as in nondestabilized events the considered digit had to be either closer or more distant to the preceding breach than in destabilized events.

Additionally, to ensure powerful contrasts in the functional analyses all modeled events [breaches (B), color events, nondestabilized events (NDE), destabilized events (DE), and resting (R)] were separated by at least 6.3 s, i.e., by nine sequential elements. The length of the whole fMRI experiment was 51 min.

Procedure

Before entering the fMRI session, each participant learned one out of the four 24-digit sequences described above. First, they received their sequence in the context of the experimental instructions. Participants were then asked to reproduce the sequence aloud. Finally, they were required to execute a 2-choice task in which the 24-digit sequence was presented 50 times digit by digit (resulting in 1,200 trials/responses). The sequential target was randomly presented with a distractor side by side and participants were asked to indicate the target by pressing the corresponding response key within 3,000 ms. Responses

were followed by a valid feedback (correct, incorrect, no answer) (600 ms) and a fixation phase (400 ms). Error rates of this 2-choice task were lower than 2% (mean = 1.79; SD = 1.06). Afterwards, participants were familiarized with the procedure of the experimental task (omission detection) and the control task (color detection) outside the scanner by performing a parallel version of the fMRI tasks. Totally, 24 out of 34 participants reached a detection rate of higher than 85% and were invited to the scanner session.

FMRI Data Acquisition

In the fMRI session, subjects lay supine on the scanner bed with their right index finger positioned on the response key. To prevent postural adjustments, the subjects' arms and head were stabilized with form-fitting cushions. Participants were provided with earplugs to attenuate scanner noise. Additionally, headphones attenuated scanner noise and provided the option to instruct participants vocally.

Imaging was performed at a 3 Tesla Scanner (Siemens Magnetom TRIO, Erlangen, Germany) equipped with the standard birdcage head coil. Twenty-eight axial slices (field of view 200 mm; 64 × 64 pixel matrix; thickness 4 mm; spacing 0.6 mm) parallel to the bicommissural line (AC-PC) were acquired using a single shot gradient echo-planar imaging (EPI) sequence (echo time 30 ms; flip angle 90°; repetition time 2,000 ms) sensitive to blood oxygenation level dependent contrast. A set of two dimensional (2D) anatomical images was acquired for each subject immediately after the functional experiment, using a T1-weighted 2D-FLASH sequence (28 slices; field of view 200 mm; 128 × 128 pixel matrix; thickness 4 mm; spacing 0.6 mm). In a separate session, high resolution whole-brain images were acquired from each subject to improve the localization of activation foci using a T1-weighted three dimensional (3D) segmented Modified Driven-Equilibrium Fourier Transform (MDEFT) sequence covering the whole brain (128 slices; field of view 256 mm; 256 × 256 pixel matrix; thickness 1 mm; spacing 0.25 mm).

FMRI Data Processing

Functional data were motion corrected with the Siemens motion correction protocol (Siemens, Erlangen, Germany). Further processing was performed using the software package LIPSIA [Lohmann et al., 2001]. To correct for the temporal offset between the slices in one volume, a cubic-spline-interpolation was applied. Temporal highpass filtering with 1/90 Hz was conducted to remove all slowly varying unwanted signals. Spatial smoothing was performed with a Gaussian filter of 5.65 mm FWHM (full width half maximum). To align the functional data slices with a 3D stereotactic coordinate reference system, a rigid linear registration with six degrees of freedom (three

rotational, three translational) was performed. The rotational and translational parameters (transformation matrix) were acquired on the basis of the MDEFT and T1-weighted 2D FLASH slices to achieve an optimal match between these 2D slices and the individual 3D reference data set. The MDEFT volume data set was standardized to the Talairach stereotactic space [Talairach and Tournoux, 1988]. The transformation matrix was subsequently normalized by linear scaling to the standard size. The resulting parameters were then used to transform the functional slices using trilinear interpolation, so that the resulting functional slices were also aligned with the stereotactic coordinate system. This normalization process generated isotropic voxels with a spatial resolution of 3 mm × 3 mm × 3 mm (27 mm^3).

The statistical evaluation was based on a least-squares estimation using General Linear Models (GLM) for serially autocorrelated observations [Worsley and Friston, 1995]. Pre-coloring was used, i.e., temporal Gaussian smoothing (4 s FWHM) was applied, which imposed a temporal autocorrelation that determines the degrees of freedom [Worsley and Friston, 1995]. The duration of modeled events was 1 s, only the 20 null-events were modeled with a length of 7 s. The design matrix was generated by hemodynamic modelling using a gamma function and its first derivative. Afterwards, contrast images were generated for each participant. The single subject contrast images were then entered into a second-level random effects analysis. The group analysis consisted of one-sample t-tests across the contrast images of all participants that indicated whether observed differences between conditions were significantly distinct from zero. In order to correct data for multiple comparisons, t-values were subsequently transformed into z-values based on the degrees of freedom determined by the sample size and on the corresponding P-value as an intermediate step. To avoid false positive activations, group z-maps were thresholded at a z-value of $z = 2.33$ ($P = 0.01$, one-tailed) and in a second step corrected for multiple comparisons using cluster-size and cluster-value thresholds obtained by Monte-Carlo simulations at a significance level of $P = 0.05$ [Lohmann et al., 2008].

In the employed GLM, breaches, color events, nondestabilized events, destabilized events, and resting periods were modeled. Destabilized events were only modeled if the preceding breach was detected by the subject, i.e., indicated by key press. Moreover, destabilized and nondestabilized events entered the model only if there was no (further) breach or color event in the preceding nine stimuli. The effect of prediction was revealed by the additive conjunction of the two contrasts nondestabilized events vs. breaches and nondestabilized events vs. resting (NDE>B ∩ NDE>R). The effect of temporally remote destabilization of prediction was revealed by the contrast of destabilized events vs. nondestabilized events (DE>NDE). To ensure that deactivation in this contrast can be interpreted as attenuation of prediction this contrast was exclusively masked by the effect of prediction contrast (NDE>B ∩ NDE>R).

RESULTS

Behavioral Results

Behavioral data were analyzed with the software SPSS (SPSS Statistic 17.0, IBM, Chicago, IL). Participants detected breaches (87.1%; SD = 10.8) to a lesser extent than color events (98.9%; SD = 2.1) ($t_{19} = 5.22$; $P < 0.001$). Mean response times (RT) of breaches (911.1 ms, SD = 182.2) were slower than that of color events (482.8 ms; SD = 57.7) ($t_{19} = -13.42$; $P < 0.001$). Behavioral results for destabilized events and nondestabilized events were not assessable as those events were sequence-congruent events that could not be responded to by participants (compare Methods).

FMRI Results

The conjunction of the contrasts nondestabilized events vs. breaches and nondestabilized events vs. resting (NDE>B ∩ NDE>R) evoked activity in the dorsal fronto-median cortex comprising Brodmann Area (BA) 10 and BA 9. Activation extended into the anterior parts of the lateral BA 8 of the superior frontal gyrus bilaterally (Fig. 1A, Table I). Further, the left superior temporal sulcus was activated (BA 38, BA 21). Furthermore, uncorrected results revealed activation in the retrosplenial area and in the parahippocampal gyrus with extensions into the hippocampus and into the collateral sulcus (Fig. 1B).

The contrast of destabilized events vs. nondestabilized events ((DE>NDE) masked with (NDE>B ∩ NDE>R)) revealed significant activation in the dorsal frontomedian cortex (BA 9 and BA 10) extending into the left and right superior frontal gyrus (BA 8 and BA 9) in favor of nondestabilized events (Fig. 1C, Table II). This effect was not modulated by the size of the preceding omission, as was tested by modelling data with this additional parameter time-locked to the onset of destabilized events. As can be seen in Figure 1, the dorsal frontomedian area being attenuated by temporally remote destabilization largely overlapped with that identified for the effect of prediction. Note that when unmasked, there were no significant activations in favor of destabilized as compared to nondestabilized events.

DISCUSSION

The neural signatures of breaches of expectancy and their instantaneous effects have been intensively investigated, while temporally more remote effects have been neglected so far. The present fMRI study explored the brain correlates of temporally remote transient destabilization of prediction following rare breaches of expectancy. Subjects were asked to monitor a cyclically running 24-digit sequence for occasional omissions of one or several digits and to immediately indicate these events by key press. Destabilization of prediction was expected to be
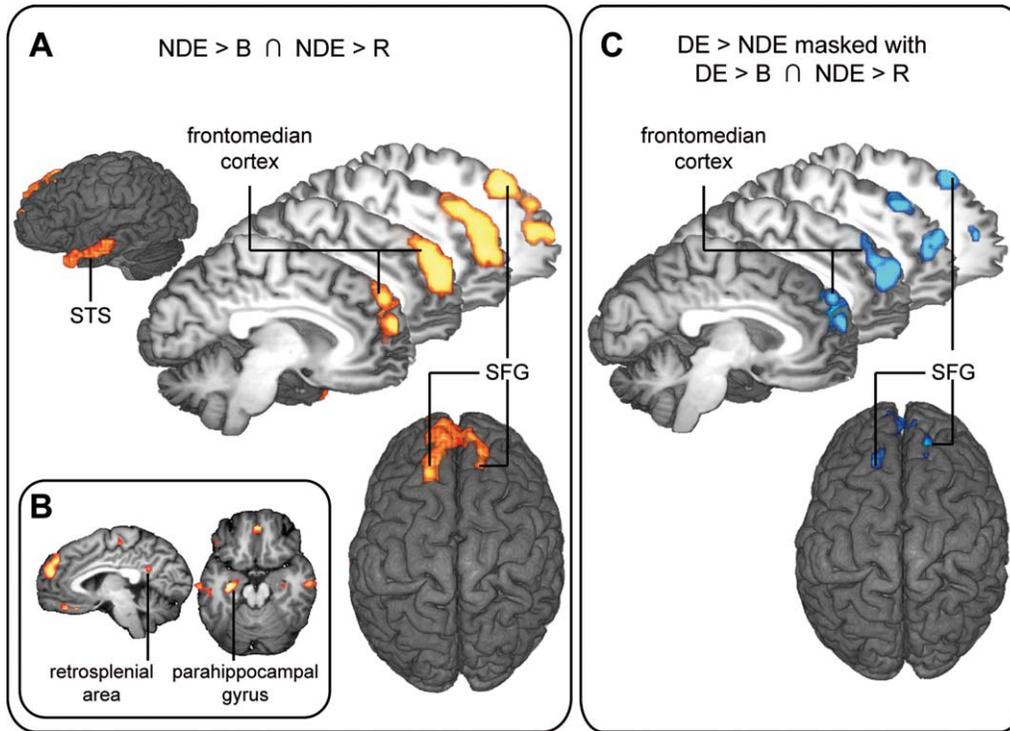
Figure 1.

Group averaged BOLD activity; **A**: activity related to prediction revealed by the conjunction of NDE > B and NDE >R , thresholded at $z = 2.33$ ($P = 0.01$), corrected for multiple comparisons ($P < 0.05$). **B**: Same conjunction as shown in A, but thresholded at $z = 2.33$ ($P = 0.01$), uncorrected, parasagittal slice at $x = -5$, axial slice at $z = -12$. **C**: Effect of temporally remote destabilization of prediction revealed by the contrast DE > NDE (masked with the conjunction of NDE > B and NDE > R) that implies predictive differences between the two categories of expected events (thresholded at $z = 2.33$ ($P = 0.01$), corrected for multiple comparisons ($P < 0.05$)). In (A) and (C), parasagittal slices cut at $x = 5$, $x = -5$, $x = -9$, and $x = -14$ (foreground to background). SFG, superior frontal gyrus; STS, superior temporal sulcus; NDE, nondestabilized events; DE, destabilized events; B, omissions (breaches of expectancy); R, resting.

TABLE I. Activation related to prediction revealed by NDE > B ∩ NDE > R (blobs with $z > 2.33$ ($P < 0.01$) and blob size > 270 mm^3); Brodmann area (BA), Talairach coordinates (x, y, z), volume (mm^3), maximal z-values (z) of significant activations, and local maxima (l.m.)

Area	BA	Talairach coordinates			mm^3	z-value
		x	y	z		
frontomedian cortex	10	−14	51	18	10368	3.67
		7	54	18	l.m.	2.93
	9	−5	48	33	l.m.	3.15
		7	51	36	l.m.	2.85
superior frontal gyrus	8	−14	30	45	l.m.	3.66
		13	36	42	l.m.	2.97
superior temporal sulcus	38	−53	12	−27	2511	3.09
	21	−50	−24	−9	l.m.	2.74

revealed by contrasting digits whose equivalent was omitted in the preceding sequential run n-1 (destabilized events) with digits without this history (nondestabilized events). Thus, effects of temporally remote destabilization of prediction were measured 14 s (on average) after a breach of expectancy occurred.

Temporally remote destabilization of prediction was reflected in an attenuation of activity in the dorsal frontomedian cortex, with a maximum in BA 9 extending partly into BA 10 and, to a lesser degree, BA 8. Importantly, the same area was also found to respond more strongly to nondestabilized events than to breaches. The uncorrected version of the latter contrast additionally revealed activation in the retrosplenial cortex and in the left parahippocampal gyrus, pointing to a memory-related network.

We take the revealed attenuation in the dorsal frontomedian cortex to reflect a destabilization of prediction. However, as participants were familiar with the omission task

TABLE II. Activation of the effect of temporally remote destabilization of prediction revealed by DE>NDE masked with NDE > B ∩ NDE > R (blobs with z < −2.33 (*P* < 0.01) and blob size > 270 mm³); Brodmann area (BA), Talairach coordinates (*x, y, z*), volume (mm³), and maximal z-values (z) of significant activations, and local maxima (l.m.)

Area	BA	Talairach coordinates			mm³	z-value
		x	*y*	*z*		
frontomedian cortex	9/10	−2	51	24	5265	−3.95
	9/10	7	54	24	l.m.	−3.68
superior frontal gyrus	8/9	−11	30	48	l.m.	−3.18
	8/9	13	39	42	l.m.	−2.96

before entering the fMRI session, one could also suspect that this decreased activity reflects quite the contrary, i.e. increased security; this is because participants could be fairly certain that omissions would most probably not reoccur at the same position as in the previous sequential run (this was actually the case in only 4% of all omissions, i.e. 6 out of 148). Importantly, this interpretation can be ruled out on the basis of the contrast nondestabilized events vs. breaches. This contrast showed higher activation in the dorsal frontomedian cortex for nondestabilized events. If certainty would have been increased at destabilized events, they should show more rather than less activity in this area when compared to nondestabilized events. However, as we found exactly the opposite pattern, the revealed attenuation can be considered reflecting a (temporally remote) destabilization of prediction.

Temporally remote destabilization of prediction was related to a decrease of activity in areas that are associated with the retrieval of sequential knowledge from long-term memory, whereas our findings do not lend support to an increase of activity in areas related to the encoding of the current stimulus. On the contrary, signal change analyses at parietal coordinates determined on the basis of the breach effect ($x = −29$, $y = −45$, $z = 39$ and $x = 40$, $y = −42$, $z = 45$) revealed no BOLD increase for the destabilized events, but rather activity comparable with nondestabilized events. We cannot rule out that compensatory increase at parietal sites was too transient to become significant, or that such modulations may have occurred in a phase following the destabilized event rather than coinciding with the event itself (note that in the latter case, this phase cannot be modelled independently from the destabilized event itself). However, we suggest that while breach-induced destabilization is the status of the internal model when entering the "destabilized event," it is by experiencing the destabilized event (that complies with the learned sequence) that the internal model is stabilized or restrengthened again. Attenuation of top-down modulation exerted by dorsal frontomedian areas may reflect a

less expectation-restricted encoding of the ongoing stimuli, which does not necessarily require enhancement of activation at parietal sites. Parietal activation observed at breaches may more specifically reflect the mismatch between incoming stimulus and internal model.

As a caveat, the comparison between nondestabilized and either unexpected digits or digits whose probability is temporarily degraded due to a preceding violation does not allow for a clear distinction between attenuation in the case of unexpected or less expected digits and an increase of activation in the case of expected ones. However, as expected digits were by far more frequent, activity in the frontomedian cortex was probably saturated in the case of expected digits and transiently attenuated in the case of unexpected or less expected ones.

The subsequent discussion will focus on studies that reported activation of medial BA 9 in paradigms using sequential stimuli, and particularly on those that require the comparison of an actual stimulus with long-term memory. Paradigms that target the build up of expectancy with regard to sequential stimuli and against the background of long-term mnemonic representation are, on the one hand, serial reaction time tasks (SRT task, Nissen and Bullemer, 1987] using spatial stimuli, and, on the other hand, paradigms that require the retrieval of action script knowledge using more complex stimuli like texts. Even though the latter studies belong to different strands of research such as text comprehension or action planning, they share, with this study, the requirement to retrieve temporally structured information from long-term memory.

In implicit sequential learning tasks like the SRT task, the dorsal frontomedian region around BA 9 has been reported for predictable as compared to random sequences [van der Graaf et al., 2006; Werheid et al., 2003] and for increasing practice of sequential responses [van der Graaf et al., 2006]. As in this study, Werheid et al. [2003] reported the retrosplenial area to be coactivated with the dorsal frontomedian wall. These areas are interconnected via reciprocal projections of the dorsal limbic pathway [Morris et al., 1999; Pandya et al., 1971; Petrides and Pandya, 1999, 2007; Schmahman and Pandya, 2009]. Whereas the retrosplenial area has been related to memory retrieval in imaging studies using different stimulus material and modalities like words, pictures, and voices [Henson et al., 1999; Shah et al., 2001; von Zerssen et al., 2001; Wiggs et al., 1999] and in neuropsychological studies on retrosplenial amnesia [Bowers et al., 1988; Valenstein et al., 1987], the special function of medial BA 9 remains unclear. In the studies of Werheid et al. [2003] and of van der Graf et al. [2006], the medial BA 9 was related to the prediction of stimuli and to the selection of appropriate responses, an interpretation that can be related to projections from the BA 9 to the premotor cortex, the supplementary motor area, and the cingulate motor area [Bates and Goldman-Rakic, 1993]. In contrast to the implicit sequencing required in the SRT paradigm, the present paradigm was an explicit sequencing task and subjects decided to press

or not to press a key rather than choosing the correct key within several possible ones. However, the requirement to predict upcoming stimuli is reflected in faster responses in both paradigms. More generally, the present data corroborate previous findings of sequential learning tasks in that the activation of the medial BA 9 can be related to the successful prediction of upcoming stimuli.

A network of dorsal frontomedian cortex and long-term memory-related areas like the retrosplenial cortex and the parahippocampal gyrus [Petrides and Pandya, 2002; for review: Simons and Spiers, 2003] akin to the one revealed by the present study has also been reported in studies on text comprehension [Ferstl and von Cramon, 2001, 2002; Siebörger et al., 2007; Xu et al., 2005; Yarkoni et al., 2008]. Obviously, compared with the present digit sequence, text comprehension calls for more complex speech-related computations, such as syntactic ones. However, texts and the present stimulus sequence are similar in their temporal properties. Texts might be considered as sequences of sentences that are related to each other with regard to temporal succession and semantic content. Moreover, text comprehension can only be successful if (a) previous sentences are maintained in short-term memory and (b) their content can be linked to prior acquired knowledge. The same applies to the present task: a single digit could be judged as matching the prediction if (a) the previous digits were maintained and (b) sequential knowledge could be retrieved.

Notably, the BOLD activity in the dorsal frontomedian cortex was higher for reading correctly ordered sentences compared with incorrectly ordered sentences of narratives [Xu et al., 2005; Yarkoni et al., 2008] as well as for sentence pairs explicitly judged to be temporally coherent compared with incoherent [Ferstl and von Cramon, 2001; Ferstl and von Cramon, 2002]. Therefore, this region's activation seems to vary as a function of temporal coherence of stimuli on the basis of knowledge derived from the readers' long-term memory. Further studies on text comprehension revealed that the activation of the medial BA 9 also varies as a function of the demands on building temporal coherence [Ferstl et al., 2005; Hasson et al., 2007; Kuperberg et al., 2006; Sieörger et al., 2007]. Kuperberg et al., [2006] reported mesial BA 9 to be most strongly activated by an intermediate level of coherence, as in contrast to either noncoherent or well-coherent texts. Authors suggested that activity in the dorsal frontomedian cortex is triggered by the detection of incoherence as indicated by lateral cortical areas, and to reflect the subsequent search for coherent relationships. This assumption is in line with results and interpretation of Ferstl et al. [2005] and Hasson et al. [2007]. In both studies, participants had to read short narratives formed by several sentences. Incoherence was generated by insertion of a single semantically incoherent word and suggested to trigger a retrieval process of previously maintained sentences in order to repair the otherwise coherent information. However, this repair process may not be triggered in entirely incoherent texts or sentence pairs [Ferstl and von Cramon, 2001, 2002; Xu et al., 2005; Yarkoni et al., 2008]. In sum, studies on text comprehension suggest medial BA 9 to be engaged either when coherence is attended to or when stimuli trigger coherence building (for review: Ferstl, 2010]. This view dovetails with the findings of neuropsychological studies on patients with prefrontal lesions [Sirigu et al., 1995, 1996] as well as imaging studies [Krueger et al., 2007; Partiot et al., 1996] that require judging the temporal order of single acts making up daily routines such as e.g., attending a restaurant or planning a trip that point to an engagement of the frontomedian cortex in the processing of action scripts. These studies highlight the importance of attending to coherent if-then relations of single acts making up more complex event scripts. This study extends these findings in that dorsal frontomedian cortex is found to be related to coherence of temporal succession not only in stimuli calling for complex linguistic computations or script knowledge, but even in stimuli of much lower complexity.

Importantly, in contrast to the present study in which temporally remote effects of breaches of expectancy were addressed, a large body of studies has focused on the immediate neural effects of breaches of expectancy. Activity of the cingulate cortex was interpreted as top-down modulation resulting in a more focused behavior [Botvinick et al., 2004] and in a slowing of responses [Botvinick et al., 2001; Coles et al., 1995]. Regarding the immediate evaluation of unexpected stimuli, electroencephalography was often used to assess slow potentials that reflect deviants; for instance, in auditory stimulus sequences of different pitches evoking the P300 [Polich, 2007], or in syntactically broken sentences evoking the P600 [Bornkessel-Schlesewsky and Schlesewsky, 2008; Pulvermüller et al., 2009]. Both components were interpreted as signatures of the same immediate repair or reprocess mechanism after unexpected stimuli that draw on memory retrieval (cf. Vissers et al., 2008] and have been related to activation of the anterior inferior frontal gyrus (BA 47) (cf. Bubic et al., 2009, 2010; Kompus et al., 2010].

This study indicates that besides the described immediate top-down modulations, temporally more remote top-down modulations that may enable the adaptation of prediction in the long run exist as well. It remains to be investigated how immediate and temporally remote effects of breaches of expectancy interact. For instance, breaches of expectancy registered at parietal sites may be immediately conveyed to the anterior cingulate cortex and to corresponding projection sites in the lateral prefrontal cortex (lateral BA 9/46 and BA 47), which in turn communicate this event to long-term expectation via frontomedian cortex (mesial BA 9) and its hippocampal or parahippocampal targets. In the case of repeated breaches of expectancy, the corresponding entry into long-term memory may be adapted and expectation modified accordingly. The adaptation of the internal model in the long run was not addressed by the present study, and hence repeated breaches at equivalent positions in subsequent sequential

runs were underrepresented in the experimental design (6 out of 148 breaches). As pointed out earlier, the revealed attenuation is suggested to be a signature of destabilization and the destabilized event itself is suggested to re-strengthen the internal model. However, future studies should implement recurrent violations at equivalent positions in subsequent sequential runs, thereby enabling a direct comparison of adapting the learned model in case of recurrence and restrengthening the learned model in case of no recurrence (as in the present study).

The present results suggest that the dorsal frontomedian cortex, and mesial BA 9 in particular, supports the retrieval of temporally structured sequential events and the prediction of sequential progression. The observed decrease of dorsal frontomedian cortex and long-term memory-related projection sites may enable adjustments of expectations or routines in the sense of a gating mechanism. According to this view, a decrease of this activation reflects an abatement of memory-based top-down modulation on current perceptual processes, and hence the promotion of a less expectation-restricted encoding of the ongoing and upcoming stimuli enabling the adaptation of expectation and prediction.

ACKNOWLEDGMENTS

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