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The effect of self-generated versus externally generated actions on timing, duration, and amplitude of blood oxygen level dependent response for visual feedback processing

Eleftherios Kavroulakis[1] | Bianca M. van Kemenade[1,2] | Belkis Ezgi Arikan[3] | Tilo Kircher[1] | Benjamin Straube[1]

[1]Department of Psychiatry and Psychotherapy, Philipps University Marburg, Marburg, Germany

[2]Institute of Neuroscience and Psychology, University of Glasgow, Glasgow, UK

[3]Department of Psychology, Justus-Liebig University Giessen, Giessen, Germany

Correspondence
Eleftherios Kavroulakis, Department of Psychiatry and Psychotherapy, Philipps University Marburg, Marburg, Germany.
Email: terryka21985@gmail.com

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Abstract

It has been widely assumed that internal forward models use efference copies to create predictions about the sensory consequences of our own actions. While these predictions have frequently been associated with a reduced blood oxygen level dependent (BOLD) response in sensory cortices, the timing and duration of the hemodynamic response for the processing of video feedback of self-generated (active) versus externally generated (passive) movements is poorly understood. In the present study, we tested the hypothesis that predictive mechanisms for self-generated actions lead to early and shorter neural processing compared with externally generated movements. We investigated active and passive movements using a custom-made fMRI-compatible movement device. Visual video feedback of the active and passive movements was presented in real time or with variable delays. Participants had to judge whether the feedback was delayed. Timing and duration of BOLD impulse response was calculated using a first (temporal derivative [TD]) and second-order (dispersion derivative [DD]) Taylor approximation. Our reanalysis confirmed our previous finding of reduced BOLD response for active compared to passive movements. Moreover, we found positive effects of the TD and DD in the supplementary motor area, cerebellum, visual cortices, and subcortical structures, indicating earlier and shorter hemodynamic responses for active compared to passive movements. Furthermore, earlier activation in the putamen for active compared to passive conditions was associated with reduced delay detection performance. These findings indicate that efference copy-based predictive mechanisms enable earlier processing of action feedback, which might have reduced the ability to detect short delays between action and feedback.

KEYWORDS
action prediction, basis function, dispersion derivative (DD), efference copy, predictive mechanisms, temporal derivative (TD)

1 | INTRODUCTION

Processing and evaluating sensory input signals requires time. Efference copy-based predictive mechanisms allow fast processing of action-feedback by generating predictions about the future state of the system before sensory feedback becomes available (Blakemore et al., 1998, 1999; Haggard et al., 2002; Wolpert et al., 1995). Interestingly, predictable sensory stimuli are often perceived as less intense compared to unpredictable stimuli (Shankman et al., 2011). When comparing self-generated (active) movements with externally generated (passive) movements, this effect is referred to as sensory suppression or attenuation (Blakemore et al., 1999).

On the neural level, this effect has been associated with weaker blood oxygen level dependent (BOLD) activations in sensory areas (Blakemore et al., 1998; Gentsch et al., 2012; Martikainen et al., 2005). It has been suggested that this phenomenon is based on an internal forward model which uses efference copies to generate predictions about the sensory consequences of our own actions (Miall & Wolpert, 1996; Sperry, 1950; von Holst & Mittelstaedt, 1950; Wolpert & Flanagan, 2001). These predictions are then compared with the actual sensory feedback. In case of a match, the self-generated stimuli are correctly predicted and less surprising than externally generated stimuli, leading to perceptual and neural sensory attenuation. Although neural attenuation in voluntary movements versus externally generated movements is well established, there are different explanations for this phenomenon ranging from cancellation to preactivation (for review, see Press et al., 2020; Thura & Cisek, 2017) and opposing theory idea (Press et al., 2020). The cancellation account expresses that when the predicted sensory effect and the actual effect are matched, that leads to sensory attenuation (Bays et al., 2006; Bays & Wolpert, 2007; Blakemore et al., 1998). The preactivation account states that the execution or the preparation of an action preactivates the sensory areas representing the expected effect related with the action as if it was actually perceived (Kühn & Brass, 2010; Roussel et al., 2013). As a consequence, when expected and actual effect match, the sensory consequences of the action are attenuated (Bäss et al., 2008; Cardoso-Leite et al., 2010) and are perceived earlier (Haggard et al., 2002; Waszak et al., 2012). Finally, the opposing theory idea makes clear predictions about the temporal evolution of perception and specifically about preactivation of the neural units which tuned toward the expected stimulus (Press et al., 2020). In the case of an unexpected event, neural units which tuned toward the unexpected stimulus are later activated and are used to update our predictions.

The temporal aspects of the hemodynamic response in the different regions of the action perception network for active as opposed to passive movements are poorly understood. Investigating relative timing of activity between conditions and brain areas aids in understanding the sequence of processing across multiple activated areas, interpreting amplitude differences, and might contribute to explaining behavior.

Over the last decades, event-related cortical potential studies (recording during movement preparation) showed increased cortical activity prior to self-initiated movements and little or no early activity in movements that are externally triggered (Cunnington et al., 1995; Jahanshahi et al., 1995; Papa et al., 1991). Moreover, it is believed that this preparatory movement activity is initiated predominantly in the supplementary motor area (SMA) (Jahanshahi et al., 1995). Specifically, rostral SMA plays a central role in movement preparation, while caudal SMA is involved in motor execution (Jenkins et al., 2000). Few fMRI studies have investigated the timing of hemodynamic response for feedback processing of active as opposed to passive movements. In one study, pre-SMA was activated earlier for self-paced movements compared to movements triggered in response to an auditory cue, reflecting involvement of this region in early processes associated with the preparation for voluntary movement (Cunnington et al., 2002). Another fMRI study examined the sequential activation of motor areas in self-paced complex movements or in response to external auditory cues; it was shown that activation in rostral SMA occurred 0.7 s earlier than in motor cortex (MI) in the externally cued execution, and 2 s earlier in the spontaneous execution movement (Weilke et al., 2001). This pointed out that timing of rostral SMA activation precedes activation in MI by different time intervals depending on the form of movement initialization. Another fMRI study investigated the temporal sequence of the hemodynamic response of SMA, visual areas and motor cortices by calculating the latencies of the hemodynamic response function (HRF) for each of the different brain areas during a visuomotor execution task. They found that the timing of cortical activation begun in the visual areas, followed by the SMA (preparatory phase) and finally by the motor cortex (movement initiation) (Mohamed et al., 2003). All these studies have investigated the timing of neural processing related to movements that were always self-initiated, either cued or self-paced. Although such a comparison might pinpoint effect of volition on the timing of movements and their sensory feedback, it cannot address the role of efference copy mechanisms. The goal of the present study is to test the hypothesis that forward model prediction leads to earlier and shorter processing of feedback from voluntary actions. In our fMRI reanalysis, which was based on data recorded in a previous study (Arikan et al., 2019; Van Kemenade et al., 2019) we incorporated real-time and delayed visual feedback of active and passive movements, using a custom-made fMRI-compatible movement device (Arikan et al., 2019; Van Kemenade et al., 2019). Specifically, we examined (i) the amplitude (HRF), timing, as represented by the temporal derivative (TD), and duration as represented by the dispersion derivative (DD) of BOLD response between self-generated and externally generated movements and (ii) direct associations between these parameters with behavioral data from the delay detection task. We hypothesized that (i) predictive mechanisms lead to earlier processing of the upcoming visual feedback in active as opposed to passive conditions which possibly results in reduced neural activity for feedback processing, reflected in reduced amplitude and duration of BOLD response. Furthermore, (ii) earlier activation might correlate with reduced behavioral performance, as an earlier representation of the visual motion feedback would be perceived as temporally closer to the actual movement. Finally, (iii) we assumed that a better model fit due to

incorporation of basis functions could also reveal neurobehavioral relationships in amplitude or duration, which were not tested, absent or covert in previous conventional analyses (Arikan et al., 2019).

2 | METHODS

Participant's data were taken from a recent study of our group (Van Kemenade et al., 2019), which examined the neural processing of delayed feedback of active versus passive hand movements. Data acquisition and experimental design have been reported previously and are described in brief below.

2.1 | Participants

Twenty-three right-handed participants with no history of psychiatric or neurological disorders and no current use of psychoactive medications took part in the fMRI experiment. All participants had normal hearing and vision or corrected to normal vision. Right-handedness was confirmed by Edinburgh Handedness Inventory (Oldfield, 1971). The experiment was approved by the local ethics committee and performed in accordance with the Declaration of Helsinki (World Medical Association., 2013). Three participants had to be excluded, one due to excessive head movement and two due to technical issues, so the final sample consisted of 20 participants (9 females, age = 26 ± 3.24). All participants were trained prior to scanning in a behavioral training session.

2.2 | Equipment

A custom-made MRI-compatible passive movement device (PMD) was used for the execution of both active and passive movements (Figure 1). The device consisted of a handle that the participant could grasp and move using their wrist in the active condition (Figure 1). In passive trials, the handle was moved automatically, with approximate force of 20 N, by using compressed air (6 bar). The movement was on a circular path from left to right and back, and the angle between the start/ending and turning point was approximately 30° (Arikan et al., 2019; van Kemenade et al., 2019). There was no significant difference in movement durations between active and passive conditions. Self-generated and externally generated movements were recorded by an MRI-compatible camera (MRC High Speed, MRC Systems GmbH, Heidelberg, Germany; refresh rate: ~4 ms). The video recordings were shown to the participants on a mirror screen. Variable delays (0, 83, 167, 250, 333, or 417 ms) established in previous experiments (Schmalenbach et al., 2017; Straube et al., 2017; van Kemenade et al., 2016, 2017), were inserted between actual movements and camera images. Auditory stimuli (sine wave 440 Hz, 500 ms duration) were presented via MR-compatible headphones (MR-Confon, Optimel, Magdeburg, Germany). Detection of movement

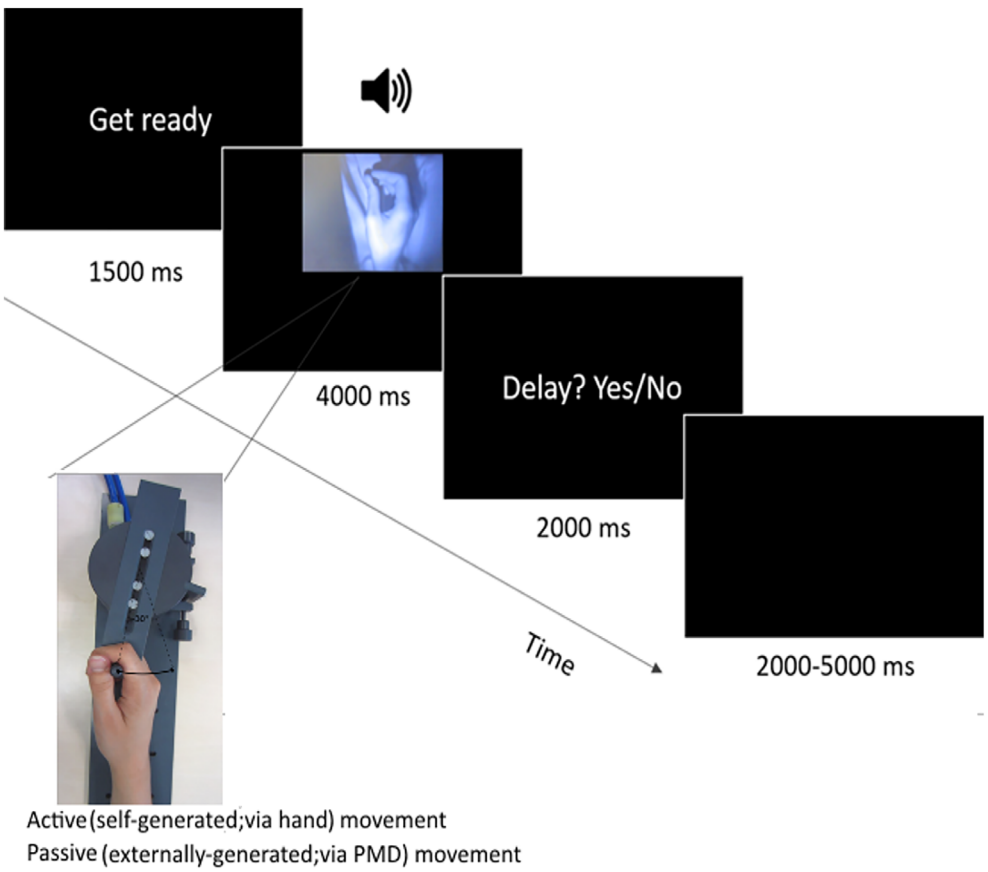


FIGURE 1 Experimental description and time frame of one trial. After the cue ("get ready"), the camera was turned on for 4000 ms and during this time window participants had to perform a voluntary (active) or an externally generated movement (passive) based on the initial guideline. Participants observed a visual display of their movement, while their task was to judge if there was a delay or not between the actual movement and the visual feedback of the movement. During bimodal trials, an auditory stimulus was additionally presented, coupled with the onset of the visual stimulus. PMD, passive movement device

onsets was achieved by infrared LEDs, attached to the device (Arikan et al., 2019; van Kemenade et al., 2019).

2.3 | Task and stimuli

The task and stimuli have been previously described (Arikan et al., 2019; van Kemenade et al., 2019). Briefly, participants performed movements with their wrist, from left to right and back, using the PMD during the active phase of the task. In the passive condition, they were instructed to hold the handle of the PMD as relaxed as possible, letting the device move their hand. Both movements were recorded by a high speed, MRI compatible camera and presented to the participants via a mirror-projection screen. Half of the trials consisted of visual feedback, while the other half consisted of both visual and auditory feedback. Both feedback types were used in the original study in order to investigate differences between unimodal and bimodal feedback. The paradigm consisted of five experimental runs. Each run was divided in passive and active blocks (with 24 trials each) in counterbalanced order. Each block started with written instructions, notifying participants about the movement they had to perform (active or passive). Each trial started with a cue, "Get ready" that lasted for 1500 ms to inform the participants that the trial was about to begin. After that, the camera was on for 4000 ms and the participants had to perform the movement during that time frame in active trials, or let the PMD execute the movement for them in the passive blocks. The onset of the passive trials was jittered (500–1500 ms). Directly afterward, the question "Delay? Yes/No" appeared on the screen and participants had to respond whether there was a delay or not, using their left index and middle fingers (button assignment was counterbalanced across participants) with maximum response time 2000 ms (Figure 1). The experiment automatically continued after 2000 ms, even when no response was given. Each run had 2 trials per delay, per condition, leading to 12 unimodal and 12 bimodal trials for each block (active/passive), and thus to 48 trials per run. Every movement was recorded and monitored online to ensure agreement with instructions and for post hoc analysis of movement durations. A behavioral training session was introduced prior to scanning, in order to familiarize the participants with the task and the equipment. Specifically, participants were shown how to perform the movements using the PMD. In order to perform the movements with a constant pace, participants were trained with a metronome. We aimed to have a complete movement (from left to right and back) in approximately 1500 ms, so we set the metronome to ~80 beats per minute. The reason for that was to discard any differences between self-generated and externally generated movements and any individual speed differences between participants. Afterward, in order to familiarize themselves with the trial sequence, participants were shown one trial for each condition without delay. After that, they performed one active and one passive training run with eight trials each (four without delay, four with the maximum delay of 417 ms, half of which were unimodal and half bimodal), in which they were informed about their delay detection performance afterward. Finally, the participants performed three runs similar to the experimental run in the scanning sessions. In these runs, a curtain was used to obscure the view of the hand, and no feedback on their performance was provided. Subjects with a detection rate of less than 50% at the 0 ms delay and a detection rate of at least 50% at the 417 ms delay participated to the fMRI experiment. Only one participant had to be excluded for not meeting the aforementioned criteria.

2.4 | Image acquisition

Functional MRI data were acquired using a 3 T TIM Trio scanner (Siemens, Erlangen, Germany), using a 12-channel head-coil. A gradient echo EPI sequence was used (TR: 1650 ms, TE: 25 ms, flip angle: 70°, slice thickness: 4 mm, gap: 15%, voxel size: 3 × 3 × 4.6 mm). For each run, 330 volumes were obtained, each containing 34 slices covering the whole brain, acquired in descending order. Anatomical images were obtained using a T1-weighted MPRAGE sequence (TR: 1900 ms, TE: 2.26 ms, flip angle: 9°, slice thickness: 1 mm, gap: 50%, voxel size: 1 × 1 × 1.5 mm).

2.5 | Behavioral data analysis

For each participant, logistic psychometric functions were fitted to the data using Psignifit (version 3) (Fründ et al., 2011). Slopes and thresholds (delay at which a 50% detection rate was reached) of the psychometric functions were extracted for each condition and used for correlations with the fMRI data. Movement onsets and offsets were determined manually using video recordings of the participants' hand in order to calculate the movement durations.

2.6 | Preprocessing and analysis

Image processing and statistical analyses were performed in SPM12 (Statistical Parametric Mapping software, SPM: Wellcome Department of Imaging Neuroscience, London, UK; available at: http://www.fil.ion.ucl.ac.uk/spm/). Realignment was applied to functional data to correct for head movement. The anatomical image of each participant was coregistered to their functional image, segmented and normalized to the standard Montreal Neurological Institute (MNI) template. The resulting parameters were then used to normalize the functional images to the MNI space (resampled to a voxel size of 2 × 2 × 2 mm). Finally, the data were smoothed with an 8 × 8 × 8 mm full-width at half-maximum kernel. A general linear model (GLM) was set up for each participant to analyze the preprocessed functional data (Friston et al., 1995). The model included regressors for each condition (active unimodal, active bimodal, passive unimodal, passive bimodal) modeling the feedback onset of the movements (active or passive) with a stick function. Also, additional regressors of the cue, the time the camera image was displayed on the screen (always 4000 ms), and the presentation of the question (until the participants answered by button

press) were included. Finally, six motion regressors of no interest were added in the final design matrix. Bimodal trials in which no tone was played or trials with no movement performed were excluded (1.4% of all trials). Hemodynamic responses were modeled by using a first- and second-order multivariate Taylor expansion of the canonical HRF (Friston et al., 1998). The partial derivatives with respect to time (TD) and duration (DD) are included in those functions. Adding this set of "basis" functions within the GLM allows estimation of the contribution of each basis function, and calculation of the mean and standard error of the best-fitting event-related response by linear combination. Specifically, inclusion of the temporal and DD within the GLM permits differences in the latency and the duration of hemodynamic response onset to be accommodated in the model and gives the opportunity to perform statistical assumptions based on latency and duration differences between conditions (Friston et al., 1998). Latencies (relative to the canonical HRF) of the BOLD impulse response were estimated via the ratio of derivative to canonical parameter estimates (Henson et al., 2002; Table 2; Figure 3(b)).

At the single subject level, T and F contrasts for the canonical and derivative terms were created for each regressor of the experimental conditions (active unimodal, active bimodal, passive unimodal, passive bimodal) against an implicit baseline. Furthermore, F and T contrasts were computed for attenuation across unimodal and bimodal conditions (passive unimodal + passive bimodal > active unimodal + active bimodal). To investigate any effect of modality, we contrasted bimodal against unimodal conditions and vice versa. We found no significant interaction of modality (bimodal vs. unimodal) by movement (active vs. passive) in amplitude, timing or duration. Therefore, we combined unimodal and bimodal into one condition both for active and passive conditions. We first examined the general effects of self-generated compared to externally generated movements on BOLD amplitude, TD and DD derivatives by using F contrasts in both single subject analyses, and at the second level using repeated-measures one-way ANOVA (Supplementary Table 1; Supplementary Figure 1).

For the second-level analyses, individual T contrasts were obtained for each of the canonical and derivative terms from each subject, yielding three contrasts per subject. These contrasts were entered into a repeated-measures one-way ANOVA model with one factor that had three levels: first for the canonical, second for the TD effects, and third for DD term. In this ANOVA, we assumed unequal variance across levels of factors to account for different variances between the canonical and derivative terms and no sphericity to account for possible across-subject correlations between the two terms. The following contrasts of interest were performed to test our hypotheses: First, we tested whether active conditions were associated with earlier BOLD responses by calculating a t-test active > passive regarding the effect of the TDs (Table 1). Second, we tested if earlier processing is related to behavioral attenuation for active versus passive conditions. Therefore, we extracted contrast estimates from the peak voxel of each significant cluster (highest *t* values at peak; see Table 1) that showed the active > passive difference. We then performed exploratory analysis (not corrected) on these extracted contrast estimates of the TDs and the behavioral threshold differences (passive–active) using SPSS 27. Then, we aimed to further understand the exact timing across different brain areas. We calculated the response latency differences (within a range of + −2 s) between passive and active conditions relative to the canonical response within several brain regions (Figure 3(b)), by estimating the ratio of the TD to the amplitude parameter estimates and transforming this ratio for each voxel with a sigmoid logistic function (Henson et al., 2002). Finally, we explored the effects of our movement manipulation (active/passive) on amplitude (active < passive: attenuation; Table 3) and duration (active < passive; Table 4) of the BOLD response by comparing conditions regarding HRF and DDs, respectively.

The above approach for estimating the amplitude ignores the potential for an amplitude bias induced by a delay difference between the hemodynamic model and the data. To diminish the effect of amplitude bias due to the use of only the nonderivative portion of the model in the test for significant amplitudes, we used the approach described by Calhoun et al. (2004), which produces an amplitude estimate that is a function of both the nonderivative and the derivative terms of the model (Calhoun et al., 2004). In this approach, the proposed amplitude test does not suffer from delay-induced bias, comprises a more natural test for amplitude differences when using a model incorporating derivative terms, while it improves the fit of the model to the data (when compared to a model not using the derivatives term).

We combined the temporal and DD to reestimate the biased amplitude regressors (computation of boosted contrast maps) (Calhoun et al., 2004; Cignetti et al., 2016; Pernet, 2014) and then used the corrected boosted contrasts at the second level (as described above). Specifically, we estimated the time-to-peak of the BOLD response voxel-wise and created a mask of the voxels whose response peak was within the specified temporal range (full range of the basis set). Furthermore, the parameter estimates were replaced with their boosted equivalents for voxels within the mask and the contrast of interest was reestimated. The code (spmup_hrf_boost.m) is available at the GitHub archive: https://github.com/CPernet/spmup/blob/master/spmup_hrf_boost.m.

Finally, family-wise error correction at $p < .05$ based on Gaussian random field theory (Worsley et al., 1996) was used, to correct for multiple comparisons at the whole brain level.

3 | RESULTS

3.1 | Behavioral analysis

Behavioral results have been reported previously (van Kemenade et al., 2019); in the present work, the focus is on associations of behavioral with fMRI data. In brief, slopes and thresholds (delay at which a 50% detection rate was reached) of the psychometric functions for each condition were evaluated. Repeated-measures ANOVAs were performed on the slopes and the thresholds with the factors modality (unimodal/bimodal) and action (active/passive). There was a significant main effect of action (Van Kemenade et al., 2019)

TABLE 1 Anatomical locations of earlier activations (TD) for self-generated (active) versus externally generated (passive) movements

		Active–passive (TD)					
Brain area	**Hemisphere**	***x***	***y***	***z***	***T***	**Cluster size**	**pFWE corr**
Precuneus	L	−12	−68	58	5.27	14	.008
Rolandic operculum	L	−50	2	14	5.24	106	.001
Thalamus	L	−10	−14	10	7.29	261	<.001
Lingual	L	−2	−70	6	5.92	247	<.001
Calcarine	L	−4	−92	6	8.09	657	<.001
MOG	L	−32	−92	6	8.49	586	<.001
MOG	R	42	−84	4	9.48	585	<.001
SOG	L	−12	−98	4	6.69	589	<.001
SOG	R	18	−98	6	7.38	490	<.001
Thalamus	R	20	−20	2	7.13	176	<.001
SFG	L	−22	50	8	6.46	108	.001
SFG	R	26	56	8	5.54	155	.007
MFG	L	−40	42	24	7.19	758	.001
MFG	R	36	58	2	6.55	1673	.001
DLPFC	R	52	12	36	6.54	1673	.000
Insula	L	−48	18	−10	5.15	16	.019
Insula	R	50	16	2	6.81	91	<.001
Putamen	L	−24	4	−8	8.73	119	<.001
Putamen	R	30	2	0	7.83	118	<.001
Caudate	L	−14	10	16	5.4	14	.001
Caudate	R	16	12	8	5.33	24	.001
ACC	L	−4	42	16	5.26	2	.033
IPL	L	−28	−50	38	5.28	4	.018
IPL	R	32	−48	48	5.47	11	.017
Postcentral	L	−52	−8	50	7.27	74	.002
Precentral	L	−50	−6	50	7.04	239	<.001
Precentral	R	40	−16	56	7.14	187	<.001
Cerebel VI	R	40	−60	−26	7.75	596	<.001
Cerebel VI	L	−36	−64	−24	6.96	384	
Cereb_crus_I	L	−38	−64	−26	6.05	7670	<.001
Cereb_crus_I	R	40	−60	−26	7.75	596	<.001
Cereb_crus_II	L	0	−82	−28	5.23	5	.036
SPL	L	−20	−56	48	5.23	43	.003
SPL	R	26	−66	32	5.13	41	.007
SMA	L	−4	12	46	7.95	232	<.001
SMA	R	12	14	44	6.98	172	<.001
Cerebel_Crus_II	R	0	−82	−28	5.23	5	.036

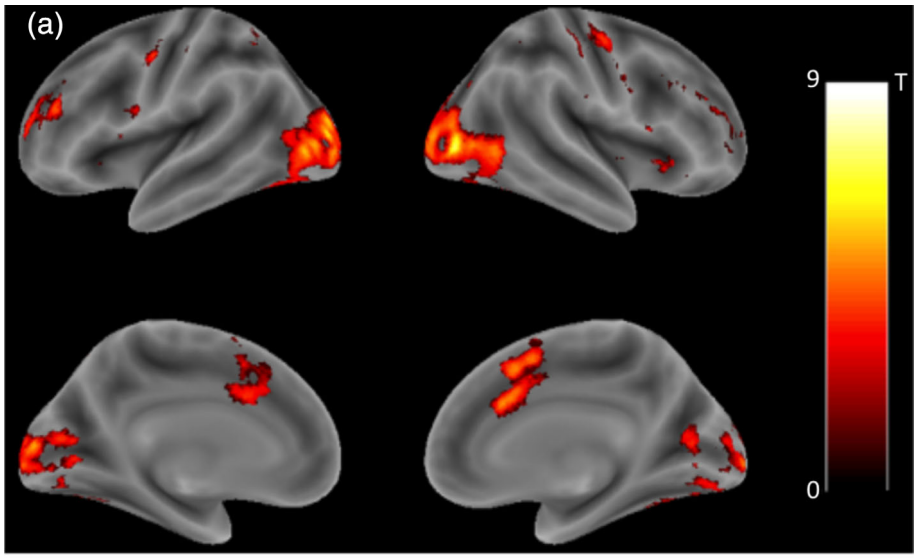
Note: pFWE < .05.

Abbreviations: ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; IPL, inferior parietal lobule; L, left; MFG, middle frontal gyrus; MOG, middle occipital gyrus; MTG, middle temporal gyrus; R, right; SFG, superior frontal gyrus; SMA, supplementary motor area; SOG, superior occipital gyrus; SPL, superior parietal lobule; TD, temporal derivative.

with lower threshold and thus better performance on passive trials, in the absence of a significant main effect of modality or a two-way interaction (Van Kemenade et al., 2019). Also, no significant main effects using the slopes were found, neither effect of action or of modality or interaction (van Kemenade et al., 2019).

3.2 | Timing of externally generated versus self-generated movements

We revealed an active > passive difference for the effect of the TD (Table 1), indicating earlier hemodynamic responses in active



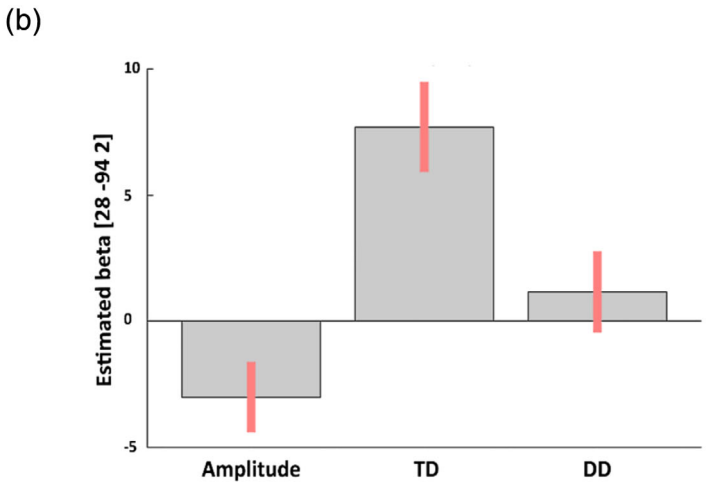


FIGURE 2 (a,b) Surface 3D brain of earlier activated areas in active as opposed to passive conditions. Bar graphs show mean beta estimates for the amplitude (negative values indicate blood oxygen level dependent [BOLD] suppression in active conditions; active < passive), temporal derivative (TD) (positive values correspond to earlier activation in active conditions; active > passive), and dispersion derivative (DD) (positive values correspond to shorter processing time in active conditions; active > passive) across participants for active as opposed to passive conditions for the peak cluster in occipital cortex. The same trend was found for most of the other activated areas

compared to passive conditions in the occipital cortex, the SMA, frontal and parietal areas, subcortical structures (bilateral putamen, thalamus, and caudate nucleus), and cerebellar areas (cerebellum crus I, II, and lobule VI) (Figure 2). Anatomical locations and detailed description of the aforementioned clusters are shown in Table 1 and Figures 2(a) and 3(a).

3.2.1 | Timing and delay detection performance

Exploratory analysis revealed positive correlations between the timing of the hemodynamic response and behavioral threshold values in the left putamen ($r = .504$, $p = .033$) in passive versus active conditions (Figure 4). This indicates that reduced delay detection performance (negative values for passive minus active) was correlated with earlier activation (negative values for passive minus active) in active versus passive conditions. We tested for the correlations of behavioral data and voxels of interest (peak voxels of each significant cluster; Table 1) and not in the whole brain. The result of this exploratory analysis is not corrected for multiple comparisons (correction for the number of peak voxels), and as such it should be interpreted with caution. No other correlations were observed between the timing of hemodynamic response and other brain regions.

3.2.2 | BOLD latency differences between self-generated and externally generated movements

We calculated the BOLD latency differences for the processing of feedback from self-generated and externally generated movements within peak clusters of different brain regions showing the active > passive difference (Table 2, Figure 5). The BOLD signal rose first in SMA, middle occipital cortex, inferior parietal lobule (IPL), and superior frontal cortex, followed by the cerebellum, precuneus, subcortical areas, middle temporal gyrus (MTG), anterior cingulate cortex, dorsolateral prefrontal cortex and rose last in the insula, superior parietal lobule, and postcentral gyrus in the active compared to the passive condition.

TABLE 2 BOLD latency differences (range +−2 s) of peak activation for feedback processing of active compared to passive movements within brain regions in three different time periods (in s) from −2 to −1; from −1 to −0.5, and from −0.5 to 0

−2 < Latencies < −1	Latencies from −1 to −0.5	Latencies from −0.5 to 0
SMA	Ang_L	Insula_R
MOG_R	Precuneus_R	Postcentral_L
SFG_R	Precuneus_L	SPL_L
IPL_R	Supramarginal_L	
Precentral_R	Thalamus_L	
	Putamen_L	
	MTG_L	
	Caudate_R	
	Caudate_L	
	ACC	
	Supramarginal_R	
	Cerebellum_R	
	Cerebellum_Crus_II	
	DLPFC	

Note: Negative values indicate earlier activation for active versus passive conditions. (pFWE < .05).

Abbreviations: ACC, anterior cingulate cortex; BOLD, blood oxygen level dependent; DLPFC, dorsolateral prefrontal cortex; IPL, inferior parietal lobule; L, left; MOG, middle occipital gyrus; MTG, middle temporal gyrus; R, right; SFG, superior frontal gyrus; SMA, supplementary motor area; SPL, superior parietal lobule.

3.3 | Amplitude and duration of BOLD responses for feedback processing of active versus passive movements

Amplitude and duration of BOLD response, reflected in the effects of the HRF and DD, respectively, were examined in externally versus self-generated movements. Attenuation (positive values for passive>active amplitudes) was observed in bilateral SMA, angular, lingual gyrus, MTG, precuneus, insula, IPL and superior frontal gyrus (SFG), as well as in the left caudate, in supramarginal and in the right cerebellum and precentral gyrus (Table 3). Significantly shorter processing time (positive values for active > passive) in active versus passive conditions was observed in MTG, caudate bilaterally and in right SFG, inferior frontal gyrus (IFG), inferior temporal gyrus (ITG), cerebellum crus II and in calcarine cortex (Table 4). Amplitude differences for comparisons not considering TD and DD have been reported earlier (see Arikan et al., 2019).

3.3.1 | Amplitude, BOLD duration, and delay detection performance

Exploratory analysis revealed negative correlations between amplitude and behavioral threshold values in the left middle occipital ($r = -.4467$, $p = .040$); lingual gyrus ($r = -.5201$, $p = .018$); SFG ($r = -.4619$, $p = .040$); putamen ($r = -.4770$, $p = .035$); rolandic operculum ($r = -.4571$, $p = .042$); precentral gyrus ($r = -.5117$, $p = .02$) and in the right precentral ($r = -.6637$, $p = .001$); and SOG ($r = -.4869$, $p = .029$) in passive minus active conditions (Supplementary Figure 2). This indicates that stronger BOLD attenuation was associated with lower delay-detection performance in active versus passive conditions. Conversely, positive correlations were observed between DD differences (reflecting BOLD duration or processing time differences) and delay detection performance. These associations were more notably in the left putamen ($r = .4455$, $p = .049$); caudate nucleus (.4922, $p = .027$); MTG ($r = .4528$, $p = .045$); cerebellum crus II (.5455, $p = .012$); rolandic operculum ($r = .4812$, $p = .031$); and right SOG ($r = .4812$, $p = .031$) (Supplementary Figure 3). Shorter processing time was associated with lower delay-detection performance in active compared to passive conditions.

4 | DISCUSSION

In the present study, we used the informed basis set of the canonical HRF (TD and DD) (1) to examine whether forward model predictions lead to earlier processing of feedback from self-generated versus externally generated actions, (2) to specify the exact timing of the BOLD response across different brain regions during self-generated versus externally generated movements, (3) to estimate hemodynamic amplitude and width differences between conditions, and finally (4) to explore how timing, amplitude and width of hemodynamic BOLD response correlate with behavioral performance. We found (1) earlier hemodynamic response in active as opposed to passive conditions. Earlier BOLD response started (2) in middle occipital gyrus, SMA, parietal, and frontal cortices followed by cerebellum and subcortical areas such as the caudate, putamen and thalamus. Confirming our previous finding of BOLD suppression in visual, sensory, premotor, and subcortical areas in active versus passive conditions (Arikan et al., 2019), we additionally found (3) shorter BOLD duration in these areas. Importantly, (4) earlier activity in the left putamen was correlated with reduced delay detection performance in self-generated versus externally generated movements. Furthermore, BOLD attenuation and shorter BOLD duration were correlated with reduced delay detection performance indicating that the consideration of TD and DD improves the sensitivity for the detection of neurobehavioral relationships compared to previous approaches (Arikan et al., 2019). Our findings indicate that predictive mechanisms enable the brain to start earlier with processing of upcoming visual movement feedback in self-generated as opposed to externally generated movements. This predictive processing might reduce the neural resources spent for feedback processing, which is reflected in a reduced amplitude and duration of the BOLD response. The observed timing differences in neural processing (active earlier = closer to the action in active compared to passive conditions) could explain the reduced delay detection performance for active compared to passive conditions.

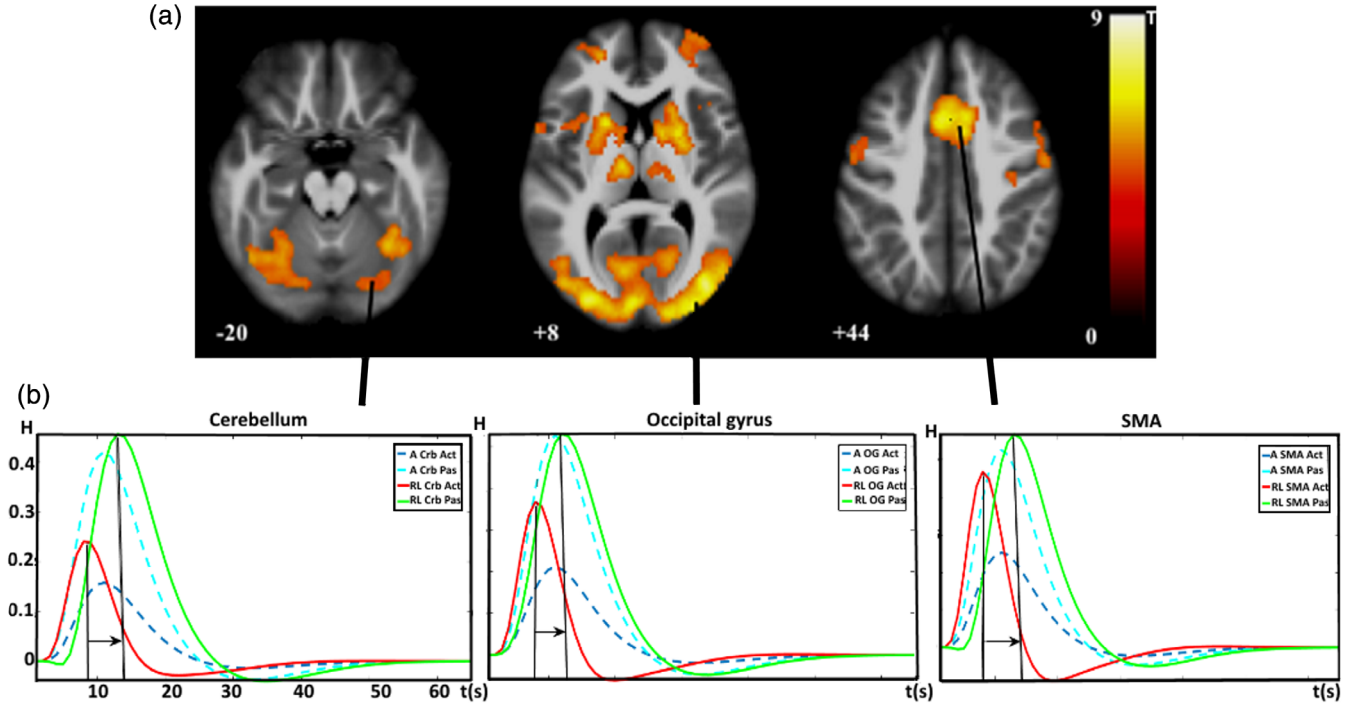


FIGURE 3 (a) Cortical and subcortical areas showing earlier activations in active as opposed to passive movements. (b) Latency functions relative to the canonical hemodynamic response function (HRF) (Henson et al., 2002) of blood oxygen level dependent (BOLD) impulse responses for active (red curve) and passive (green curve) conditions indicated that cerebellum, occipital gyrus, and SMA activated earlier in active as opposed to passive conditions (the same trend also found in the other brain areas of Figure 2(a)). The arrow indicates the time to peak difference—latency between active (red curve) and passive condition (green). The blue curve corresponds to the amplitude of the canonical HRF for active and light blue for passive conditions. While OG, SMA, and cerebellum were all activated earlier for active versus passive conditions, amplitude differences exist between the three regions, highlighting the complementary information revealed when considering HRF, temporal derivative (TD), and dispersion derivative (DD). Crb, cerebellum; H, activation height; OG, occipital gyrus; RL, relative latency; SMA, supplementary motor area; t(s), time in seconds. ($p < .05$ family-wise error [FWE] corrected)

4.1 | Earlier processing of self-generated movement feedback

In line with our hypothesis, we found earlier cortical activations in somatosensory, visual, frontal areas and also in subcortical areas and cerebellum for feedback processing of active compared to passive movements. Specifically, we found that SMA is activated earlier in active than in passive movements which might reflect a direct consequence of movement preparation, as many fMRI studies have shown increased activation of the SMA during early stages of movement preparation prior to movement onset (Lee et al., 1999; Richter et al., 1997; Sakata et al., 2017; Wildgruber et al., 1997). However, it has been also suggested that the SMA is the source of efference copy signals used in forward model predictions leading to sensory attenuation (Haggard & Whitford, 2004). Our results are also in line with this idea, as efference copy-related processes are expected to occur early to prepare sensory areas regarding the predicted feedback in active conditions.

In addition to the SMA, we found earlier activation in IPL, in SPL and in SFG for self-generated movements which is in line with another study showing that early activation in frontal and parietal cortices predicted the outcome of free decision before the participant registered awareness of those decisions (Soon et al., 2008). We also observed earlier activation in visual and auditory cortices, in the precuneus and in the insula for visual feedback processing of self-generated as opposed to externally generated movements. This is in line with a recent study that reported that these areas were activated significantly earlier during movement performed when the participant felt the urge to do it compared to movements performed in response to a visual stimulus (Sakata et al., 2017). Our results suggest that preparatory activity in sensory and visual cortices, SMA, precuneus, and insula probably prepares the brain not only for execution of the movement, but also for monitoring and processing of the expected visual and auditory consequences. Moreover, earlier activation was observed in the MTG. MTG is relevant for processing and awareness of temporal discrepancies in action feedback monitoring and likely plays a role in the transmission of information about sensory mismatches in self-generated and externally generated actions (Van Kemenade et al., 2019). However, for the aforementioned area, so far, no previous studies have demonstrated early activation during feedback processing. In addition, we found earlier activation in the cerebellum for feedback processing of self-generated as opposed to externally generated movements. It has been proposed that the cerebellum is a comparator area specific to self-generated actions (Van

TABLE 3 Anatomical locations of peak activations for feedback processing of externally (passive) versus self-generated (active) movements

		Passive–active (amplitude)				
Brain area	**Hemisphere**	***x***	***y***	***z***	***T***	**Cluster size**
Supramarginal	L	−46	−44	30	5.92	40
Angular	L	−36	−56	34	5.65	90
Angular	R	58	−58	30	5.16	21
Precuneus	R	4	−56	34	5.38	223
Precuneus	L	−4	−56	34	5.95	223
SFG	L	−22	50	8	5.92	80
SFG	R	26	56	8	6.88	441
Insula	L	−30	20	−6	7.16	166
Insula	R	30	28	−6	5.39	36
MTG	L	−48	−50	2	5.78	343
MTG	R	44	−60	2	5.90	1123
Caudate	L	−16	8	12	5.13	4
ACC	L	−2	16	22	5.20	1428
ACC	R	4	40	24	5.67	1428
IPL	L	−46	−48	36	5.33	40
IPL	R	42	−54	36	5.27	21
Cerebellum VI	R	38	−66	−30	5.68	596
Cerebellum II	R	6	−80	−34	5.19	7
SPL	L	−20	−56	48	5.31	43
SMA	L	−4	12	46	5.65	232
SMA	R	12	14	44	5.20	172
ITG	R	46	−54	−12	5.30	1123
Lingual	L	−10	−72	0	5.26	4
Lingual	R	16	−74	0	5.73	1123
MFG	L	−34	50	0	5.20	228
MFG	R	34	56	0	6.26	441

Note: pFWE < .05.

Abbreviations: ACC, anterior cingulate cortex; Cerebel, cerebellum; IPL, inferior parietal lobule; ITG, inferior temporal gyrus; L, left; MFG, middle frontal gyrus; MTG, middle temporal gyrus; R, right; SFG, superior frontal gyrus; SMA, supplementary motor area; SPL, superior parietal lobule; Supramarg, supramarginal.

TABLE 4 Anatomical locations of shorter BOLD duration (DD) during self-generated (active) versus externally generated (passive) movements

		Active–passive (DD)				
Brain area	**Hemisphere**	***x***	***y***	***z***	***T***	**Cluster size**
SFG	R	24	52	10	5.39	62
Calcarine	R	30	−68	10	5.80	38
IFG	R	−34	36	−2	5.23	20
MTG	L	−46	−14	−18	5.28	10
MTG	R	46	−48	−4	5.66	9
Caudate	L	−18	12	14	5.24	2
Caudate	R	18	20	10	5.75	22
Cerebellum II	R	4	−84	−38	5.17	3
ITG	R	48	−46	−6	5.39	9

Note: pFWE < .05.

Abbreviations: BOLD, blood oxygen level dependent; DD, dispersion derivative; IFG, inferior frontal gyrus; ITG, inferior temporal gyrus; L, left; MTG, middle temporal gyrus; R, right; SFG, superior frontal gyrus.

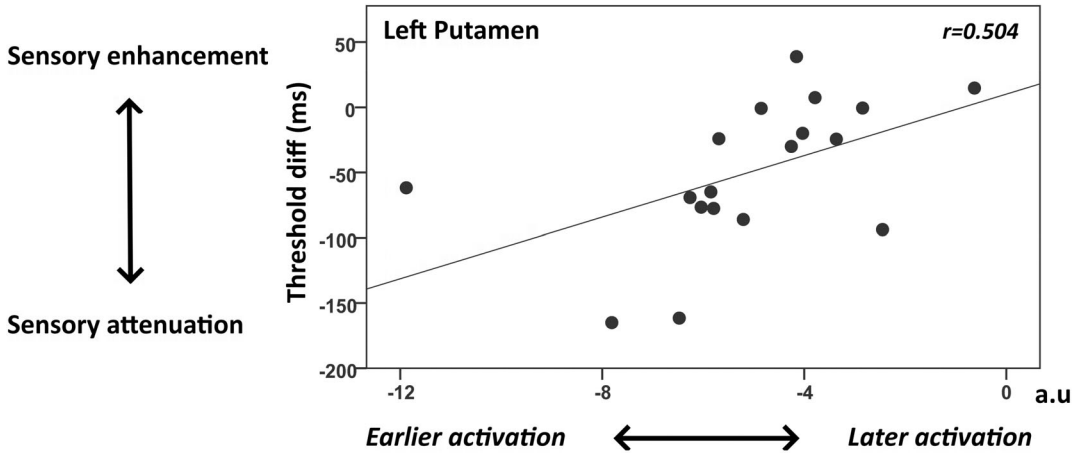


FIGURE 4 Positive correlation between the passive–active differences in timing of the hemodynamic response and passive–active differences between delay detection thresholds in the left putamen ($r = .504$ $p = .033$) indicates that reduced delay detection performance was correlated with earlier activation in active versus passive conditions. The x axis refers to the eigenvariates of the temporal derivative (TD) contrast in arbitrary units. The y axis displays the difference in threshold values (delay at which a 50% detection rate was reached) between passive and active conditions (passive–active) in milliseconds (ms). a.u., arbitrary units; ms, milliseconds; threshold diff, threshold differences

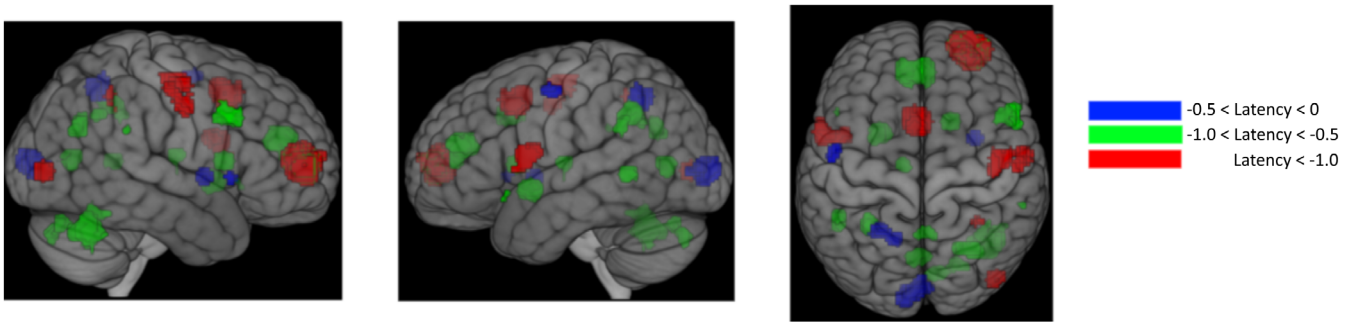


FIGURE 5 3D render brain of clusters with peak latency differences between self-generated (active) and externally (passive)-generated movements of below −1 s (red), between −1 and −0.5 s (green) and between −0.5 and 0 s (blue)

Kemenade et al., 2019) which processes sensory mismatches based on efference copy mechanisms. Earlier activity in the cerebellum in voluntary actions can be explained by the fact that a comparator area needs to build up the predicted representation in order to quickly compare the incoming with the predicted sensory information. The cerebellum has a supplementary role in planning related to detection and adaptation of visuomotor errors (Elsinger et al., 2006), processes necessary to solve our applied action-feedback delay detection task. Altogether, our findings further support the idea that the cerebellum plays an important role in predictive perception of movement feedback.

Finally, we found subcortical early activity for self-generated movements as opposed to externally generated movements. Specifically, earlier activation was observed in the caudate nucleus, putamen, and thalamus. This is in line with several other studies showing higher activation in the putamen for self-generated compared to externally triggered actions (Cunnington et al., 2002; Jahanshahi et al., 1995; Jenkins et al., 2000; Wiese et al., 2004), as those require more planning (François-Brosseau et al., 2009). Thus, subcortical brain regions associated with movement planning may therefore also be related to preparation for the processing of visual movement feedback from self-generated-movements, as indicated by our results.

Our results concerning earlier activation in frontal areas, cerebellum and striatum for feedback processing of self-generated generated movements versus externally generated ones are in agreement with the idea that caudate possibly evaluates the quality of predictions occurring in the DLPFC–cerebellum circuit, while anterior putamen and ventral striatum may evaluate the goodness of the executed actions based on sensory feedback (Fermin et al., 2016). Activation in DLPFC has been linked with sequential action planning (Doya, 1999), forward planning, and prediction of an action's future outcome (Daw et al., 2005; Dayan, 2009; Gläscher & O'Doherty, 2010; Warner et al., 2013; Wunderlich et al., 2012).

With our study we showed for the first time, that processing of feedback from self-generated movements starts earlier than processing of feedback of externally generated movements in a distributed

network of cortical, cerebellar, and subcortical structures, consisting of motor and sensory cortices, cerebellum, and basal ganglia, probably due to efference copy-based forward model predictions.

4.2 | Timing and sequencing of neural activity in self-generated movements compared to externally generated movements

Many brain regions contribute to planning and execution of movements as well as the processing of movement feedback. However, the temporal sequence of neural processing across these regions is not well investigated. If we assume that different brain regions contribute different functions or resources to a specific task, it is likely that distinct brain regions are not activated completely simultaneously, even when identified with the same contrast. We calculated BOLD latency differences (Henson et al., 2002) in peak clusters of different brain areas for feedback processing between self-generated and externally generated movements (active > passive difference). We found that activity in MOG started 1.25 s earlier for self-generated compared to externally generated movements, indicating early preparation for the processing of the upcoming visual movement feedback in active conditions. This is in agreement with a visuomotor study, in which the sequencing of cortical activation started in occipital cortices, followed by the SMA and finally by the motor cortex (Mohamed et al., 2003). Moreover, for feedback processing of self-generated movements, activity started in SMA and ACC 1 s earlier than for externally generated movements. A high-density EEG recording study reported that activity in the ACC started already 2.5 s prior to self-generated movement onset (Ball et al., 1999). Despite these differences in the exact timing, our study supports the assumption that activity in the ACC is affected by sensorimotor predictions. Also, we found that activation in cerebellum, in left putamen and in caudate started in the self-generated condition 900, 1000, and 700 ms respectively, prior to processing of feedback of externally generated movements. Previous studies reported that pre-movement activity during self-generated actions reverberates through cortex–basal–ganglia–thalamocortical loops with latencies of 200–250 ms (Klaus & Plenz, 2016; Oldenburg & Sabatini, 2015). Thus, cortex–basal–ganglia–thalamocortical loops might be relevant for efference copy-based predictions allowing early and efficient processing of predictable sensory information.

In summary, we calculated for the first time latency differences related to feedback processing, between active and passive conditions and we were able to explore the potential processing hierarchy of voluntary actions. Activity started in the occipital structures, then SMA and cerebellum, followed by an involvement of more distributed cortex–basal–ganglia–thalamocortical loops. Even though the latencies are just estimates and depend on many factors such as model fit, cluster size or size of a given brain region, this pattern is in line with the literature and suggests that predictive processes related to voluntary (compared to passive) movements affect the timing of the complete assemble of cerebella–basal–ganglia–thalamocortical regions and might even start with a visual representation in the occipital lobe.

4.3 | Attenuation and shorter processing of self-generated movement feedback

In addition to investigating the timing of neural activity differences between active and passive movements, we utilized the DD to estimate differences in processing times between conditions. We found significantly shorter processing times (DD) in active as opposed to passive movements in bilateral caudate, MTG and in right SFG, IFG, in calcarine gyrus, in ITG and in the right cerebellum crus II. Moreover, we confirmed our previous finding of reduced BOLD amplitudes indicating attenuation for self-generated versus externally generated movements (passive > active) in a widespread network involving several frontoparietal areas, as well as SMA, visual cortex, cerebellum, and subcortical structures (Arikan et al., 2019). Estimation of hemodynamic latency and width, in addition to amplitude, provides a more detailed and quantitative approach of exploring brain functions such as processing delay and relative processing time, leading to a more elaborated description of cognitive models that include relevant timing information (Bellgowan et al., 2003). While the earlier processing (TD effect) in active conditions is in line with the opposing theory (Press et al., 2020), the prediction-related reduced processing (amplitude) which goes along with reduced behavioral performance (see below), is also in line with the cancellation account which states that predicted sensory effect is subtracted from the actual effect leading to sensory attenuation when both effects are matched (Bays et al., 2006; Bays & Wolpert, 2007; Blakemore et al., 1998). An alternative explanation would be that the earlier processing leads to a temporally earlier representation of the feedback (perception that the movement on the screen occurred earlier) compared to action, reducing the ability to detect small delays. This explanation could explain the often observed temporal binding effect (Hughes et al., 2013) by predictive shifts in the temporal representation of action outcomes. We demonstrated a pattern of earlier and reduced (in amplitude and duration) processing for self-generated compared to externally generated movements. Notably, in addition to predictive mechanisms, we assume to be responsible for the observed pattern, more general motor-related aspects might have also contributed to the observed result pattern. However, if the generation of motor commands, which are absent in passive movements, would contribute to the pattern, we would expect not an earlier processing but a significant difference in amplitude (active > passive; reflecting the motor command) in the first place. Importantly, we observed suppression (active < passive) regarding the amplitude in all of the regions that show earlier processing. Thus, it is unlikely that a motor command itself is related to a reduced amplitude, but rather to the processing of the predicted feedback.

4.4 | Neurobehavioral relationships

We found timing, duration, and amplitude of the putamen to be correlated to action-feedback delay detection performance (see Figure 4 and Supplementary Figures 2 and 3). Specifically, the timing of the hemodynamic response (TD) and behavioral threshold values in the

left putamen were positively correlated. This indicates that earlier activation in putamen in active versus passive conditions was linked with sensory attenuation (worse performance in delay detection task). Furthermore, BOLD amplitude attenuation and duration of processing time (DD) in the left putamen were correlated with worse performance in detecting delays (sensory attenuation). Thus, we were able to connect this subcortical activation with action outcome monitoring, suggesting a potential role in generating predictions and preparing the brain for the likely upcoming visual information. The effort for this process seems to be low, as indicated by reduced BOLD response amplitude and duration, but occurs earlier, as indicated by the negative difference in the effect of the TD between passive and active conditions. Our approach assumes that there is default prediction of the undelayed feedback trials as they are close to everyday life experiences, so these and the very small (undetected) movement-feedback delays can be considered especially predictable in the active conditions. Consequently, BOLD suppression is strongest close to action and stronger for trials with undetected than detected delays (Straube et al., 2017). In contrast, for passive conditions, less predictable visual feedback might be responsible for increased BOLD response amplitude and duration as well as later processing which probably reflects prediction error signals. Another possible explanation is that the weights on feedback or predictions might differ between conditions and the sensory (visual and tactile/proprioceptive) feedback signals are assigned higher weights when feedforward information is limited. Thus, higher weights to sensory feedback could explain the better performance in passive compared to active conditions. However, why weights are reduced for active conditions and if this reduced weighting of sensory information could be explained by preactivation or cancellation, remains an open question.

Moreover, our results benefit from the use of basis function model, as we found correlations between BOLD amplitude attenuation (passive > active) in bilateral precentral gyrus, in left middle occipital gyrus, lingual gyrus, SFG, rolandic operculum and in right superior occipital gyrus and performance in detecting delays (sensory attenuation) in self-generated versus externally generated movements (Supplementary Figure 2), which cannot be revealed with the conventional approach as in our previous study (including the HRF amplitude only (Arikan et al., 2019)). This is in agreement with a study reporting that the use of a better fitting model has advantages (Lindquist et al., 2009), such as the identification of meaningful brain–behavioral relationships. Additionally, shorter processing time (DD) in left MTG, caudate, rolandic operculum, in right cerebellum crus II, and in SOG was correlated with worse performance in detecting delays in self-generated versus externally generated movements (Supplementary Figure 3). Earlier processing in active compared to passive movements is well in line with the opposing theory idea as it makes clear predictions about the temporal evolution of perception and allows the preactivation and attenuation mechanisms to coexist (Press et al., 2020). However, further studies on temporal aspects of predictive neural processing in relation to behavioral performance are necessary to differentiate between the different theoretical accounts and to confirm our exploratory results.

4.5 | Limitations

While the applied approach is suitable to examine whether forward model predictions lead to earlier and shorter processing of self-generated compared to external generated moments, this approach has some limitations. First, it is difficult to disentangle action and feedback-related processing in the brain. Thus, early activity for example in the premotor cortex, SMA, and cerebellum could be more related to action execution than the processing of the visual feedback. However, in this context, we think it is impossible to disentangle action and related feedback processing. The exploratory correlation analyses at least support our interpretation that areas with earlier processing are relevant for sensory feedback processing. Second, we compared different regions regarding their individual timing which could be problematic due to differences in size, location regarding slice acquisition order and anatomical properties. However, as we always compare active and passive conditions within each region, the relative timing might still be interpretable. Another important issue is that we trained participants to move at a certain speed in order to minimize movement durations between active and passive conditions, so that differences in neural activity between these conditions could not be explained by differences in the duration of the movement and sensory feedback. As a result, this might remove interindividual differences in movement speed and probably some participants had to adjust their movement planning. However, we do not think this could have affected the results much, as the focus of this article was on how action affects neural processing of action feedback. All participants had to process the sensory feedback to both monitor their movement and perform the delay detection task. Even if some had to adjust their movement planning, we still looked at how movement planning affects neural processing compared to passive movements. It could be very interesting to explore individual differences based on how close the movement speed is to someone's typical behavior, but this is beyond the scope of the current study. Nevertheless, the development of new paradigms and data acquisition procedures as well as the application of more time sensitive methods are important to validate our results and to become a complete picture about the temporal sequence of involved processing steps. Finally, reported correlation analyses were not corrected for multiple comparisons and therefore require replication in bigger samples and need to be interpreted with caution.

4.6 | Conclusion

To summarize, in line with our hypotheses, we confirmed our previous finding of reduced BOLD activation, and additionally found earlier and shorter BOLD responses in multiple cortical, subcortical, and cerebellar brain structures for active versus passive movements. Specifically, we found earlier BOLD activity in visual and somatosensory cortical areas, the cerebellum, basal ganglia, and thalamus, during self-generated as opposed to externally generated movements, indicating that efference copy-based predictive mechanisms enabled earlier processing of action feedback in self-generated movements. Such a prediction-related preactivation could

be the basis for subsequent attenuation (or cancellation) of sensory processing and thus seems to be in line with both the preactivation and cancellation accounts, as well as the opposing theory encompassing both phenomena (Press et al., 2020). Furthermore, we identified the sequencing of the neural activity during action feedback processing of self-generated movements, indicating earlier processing in occipital structures and the SMA, followed by predominantly cerebellar, parietal, and subcortical structures, followed by somatosensory areas (postcentral gyrus). Finally, we reported for the first time shorter BOLD duration in cortical and subcortical brain regions in self-generated versus externally generated movements, which was correlated with reduced delay detection performance in self-generated movements. Together, these new results highlight the relevance of considering timing and duration differences in BOLD responses when investigating action-related predictive mechanisms. Furthermore, the data suggest that the consideration of timing and duration in addition to amplitude of the BOLD response, is important to predict and understand human behavior, which are related to the different aspects of the BOLD response. Finally, our results shed new light on the cortico-cerebellar-striatal loops involved during predictive perception of the visual feedback of one's own hand movements. Together, these results provide a solid basis for investigating the role of BOLD timing and duration on impaired predictive mechanisms and action monitoring in patients with schizophrenia spectrum disorders (Blakemore et al., 2000; Leube et al., 2010; Straube et al., 2020; Uhlmann et al., 2021).

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CONFLICT OF INTEREST

The authors confirm that there are no known conflicts of interest associated with this publication.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Eleftherios Kavroulakis https://orcid.org/0000-0003-3521-9988
Bianca M. van Kemenade https://orcid.org/0000-0002-8631-9893
Belkis Ezgi Arikan https://orcid.org/0000-0001-5741-2880

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