# Free won't : neurobiological bases of the development of intentional inhibition

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# Chapter 4

# A medial-lateral distinction for intentional versus externally guided action control: Evidence from a combined heart rate and fMRI study.

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## 4. A medial-lateral disctinction for intentional versus external action control

**Abstract**

Externally and internally guided action control processes are associated with changes in both central (neural) and autonomic (heart rate) responses, but commonalities between these systems are not well understood. The present study aimed to integrate the study of heart rate and neural changes in one experiment in order to examine the role of a central autonomic network in intentional and externally guided action control. The results showed that heart rate deceleration during externally guided action control was associated with lateral PFC activation, whereas heart rate deceleration during intentional action control was associated with medial frontal cortex activation. The latter was observed for both intentional action and intentional inhibition events. Together, the results indicate that heart rate deceleration during action control is an integral part of the central autonomic network, which shows a medial/lateral distinction for intentional versus externally guided action control.

## 4.1 Introduction

The ability to exercise control over our actions is an important part of successful functioning in daily life. Action control can be guided both externally, such as when a traffic light turns red, and internally, such as when controlling the urge to scratch an itchy mosquito bite. The latter process is referred to as intentional inhibition, which can be defined as a late veto opportunity (Brass & Haggard, 2007; Filevich, et al., 2012). A host of literature has indicated that externally guided inhibition is associated with heart rate deceleration (e.g. Börger & van der Meere, 2000; van Boxtel, et al., 2001; Van der Veen, et al., 2000). Recently, heart rate deceleration has been shown to also be a sensitive index for intentional inhibition (Schel, Windhorst, van der Molen, & Crone, 2013). Together, these studies suggest the involvement of a central autonomic network in external and intentional action control, but how central and autonomic responses are related in externally and internally guided control is not well understood.

To date, most research on the neural correlates of externally versus internally guided action control has focused on intentional action selection (for a review, see Brass & Haggard, 2008). Within this domain, previous research has suggested a medial-lateral distinction for internally vs. externally guided action control, with internally guided action selection being associated with activation in medial frontal cortex and externally guided action selection being associated with activation in lateral prefrontal cortex (Brass & Haggard, 2008; Goldberg, 1985; Krieghoff, Waszak, Prinz, & Brass, 2011). The evidence for intentional inhibition is less clear. Some studies have found activation in dorsal medial frontal cortex for intentional inhibition (Brass & Haggard, 2007; Kühn, et al., 2009). However, others reported activation during intentional inhibition in lateral prefrontal cortex, in regions similar to those involved in externally guided inhibition (Schel et al., 2014).

The present study aimed to examine the involvement of a central autonomic network in intentional and externally guided action control. For this means, participants performed an action control task in the MRI scanner, while their heart rate was measured continuously. Externally guided action trials were presented intermixed with intentional action control trials, where participants could choose between acting and inhibiting. We expected to observe heart rate deceleration during intentional compared to externally guided action control (Schel, et al., 2013). Furthermore, for intentional action control we expected to find a relation between heart rate responsiveness and activation in medial frontal cortex, and for externally guided action control between heart rate responsiveness and activation in lateral prefrontal cortex (Krieghoff, et al., 2011).

## 4.2 Method

### *Participants*

Twenty-four healthy right-handed adults between 18-26 years of age participated in the experiment. Eight participants were excluded from all data analysis because of

poor quality heart rate data, caused by scanner artifacts. For these participants, it was not possible to distinguish R-waves from noise. However, when analyzing the fMRI data for the complete sample ($N$ = 24) and for the final sample ($N$ = 16), there were no differences in activation patterns, suggesting that the noisy heart rate measures were not associated with differences in neural activation. The final sample consisted of sixteen adults between 18-26 years of age (8 females, $M$ = 21.82, $SD$ = 2.43). All participants had normal or corrected-to-normal vision, and no neurological or psychiatric impairments according to self-report. Before participating in the experiment, all participants signed informed consent. All anatomical scans were reviewed by a radiologist. No anomalous findings were reported.

To obtain an estimate of cognitive functioning participants completed two subtests of the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1981a); similarities and block design. Estimated IQ scores were within the normal range ($M$ = 112, $SD$ = 7.03).

The behavioral and fMRI results of the complete sample ($N$ = 24) have been published separately in a study comparing intentional and externally guided inhibition (Schel et al., 2014).

### *Task*

The marble task was adapted from Kühn et al. (2009), and optimized for heart rate recording (Schel, et al., 2013). Each trial started with the presentation of a fixation-screen, jittered between 1400 and 2000 ms. Hereafter, a white marble on top of a ramp was shown, which started to roll down and changed color to green after a variable duration of 1400 to 2000 ms. Participants were instructed to respond to the rolling green marble to prevent it from crashing (externally guided action). Intermixed with the green marble trials, trials in which the marble remained white were presented during which participants were free to choose between responding (intentional action) and inhibiting responding (intentional inhibition) to the rolling marble. The experiment consisted of three blocks of 80 (48 green, 32 white) trials each (see Schel, et al., 2014 for further task details (chapter 3)).

### *fMRI Data Acquisition*

Scanning was performed with a standard whole-head coil on a 3.0 Tesla Philips scanner at the Leiden University Medical Center. Functional data were acquired using T2*-weighted echo-planar imaging (EPI). The first 2 volumes of each run were discarded in order to allow for equilibration of T1 saturation effects (TR = 2.2 sec, TE = 30 msec, sequential acquisition, 38 slices of 2.75 mm, field of view 220 mm, 80 x 80 matrix, in-plane resolution 2.75 mm). After the functional runs a high-resolution 3D T1-FFE scan for anatomical reference was obtained (TR = 9.760 ms; TE = 4.59 ms, flip angle = 8 degrees, 140 slices, 0.875 × 0.875 × 1.2 $mm^3$ voxels, field of view = 224 × 168 × 177 $mm^3$). Head motion was restricted by using foam inserts between the head and the head coil. Visual stimuli were projected onto a screen in the magnet bore that could be viewed through a mirror attached to the head coil.

***Heart Rate Data Acquisition and Analysis***

During scanning, the electrocardiogram (ECG) was measured continuously using the MRI-compatible Biopac System at a sample frequency of 5000 Hz. The ECG was recorded from three AgAg/Cl electrodes, attached directly around the heart. Inter Beat Intervals (IBIs) were defined as the length between consecutive R-peaks. The R-peaks were detected with the program Physiospec (developed by Van Beek, Developmental Psychology, UvA). The recorded IBIs were manually screened for physiologically impossible readings and artifacts (i.e. R-peaks not detected or other peaks seen as R-peaks). These were corrected by adjusting specific parameters in the program that extracted the IBIs from the digitized ECGs.

Five consecutive IBIs were selected around the onset of marble motion; the IBI concurrent with the onset of marble motion (IBI 0), two IBIs preceding the onset of marble motion (IBI -2 and IBI -1), and two IBIs following the onset of marble motion (IBI 1 and IBI 2). In order to obtain an index of phasic heart rate change (IBI difference) IBIs were referenced to IBI-2. Thus, we analyzed the differences scores relative to IBI -2 for IBI -1, IBI 0, IBI 1 and IBI 2. Analyses of IBI-2 revealed no significant differences in IBI length between the different test conditions, confirming that there were no a priori differences between these conditions reflected in heart rate. Statistical analyses were performed using repeated measures ANOVA. Huynh-Feldt corrections for violations of the assumption of sphericity were used when necessary (Jennings, 1987; Vasey & Thayer, 1987).

***fMRI Data Analysis***

Data were preprocessed using SPM8 (Wellcome Department of Cognitive Neurology, London). Images were corrected for rigid-body motion. Structural and functional volumes were spatially normalized to T1 templates. The normalization algorithm used a 12-parameter affine nonlinear transformation involving cosine basis functions, and then resampled the volumes to 3-mm cubic voxels. Translational movement parameters never exceeded 1 voxel (< 3mm) in any direction for any subject or scan. Templates were based on the MNI305 stereotaxic space (Cocosco, et al., 1997), an approximation of Talairach space (Talairach & Tournoux, 1988). Functional volumes were spatially smoothed with an 8-mm full-width-at-half-maximum isotropic Gaussian kernel. Statistical analyses were performed on individual participants' data using the general linear model in SPM8. The fMRI time series data were modeled by a series of events convolved with a canonical hemodynamic response function (HRF) and the temporal derivatives. The onset of marble motion of each trial was modeled as an event of interest. Separate regressors were defined for white nogo (intentional inhibition), white go (intentional action), green go (stimulus-driven action), and green omissions (omission on the green marble trials). The trial functions were used as covariates in a general linear model, along with a basic set of cosine functions to high-pass filter (120 Hz) the data. The least-squares parameter estimates of the height of the best-fitting canonical HRF for the different conditions were used in pair-wise contrasts.

To examine the relationship between heart rate and neural activation, IBI differences scores were added as regressors to the whole-brain regression analyses. All

reported correlations between heart rate and neural activation consisted of at least 10 contiguous voxels at an uncorrected threshold of $p < .001$. The reason for setting this threshold was because we had a priori hypotheses on which brain regions (lateral and medial PFC) were of interest in this study and to avoid Type II errors, because detecting individual correlations requires more power than group analyses (see also Lieberman & Cunningham, 2009). Region of interest (ROI) analyses were performed to visualize the relationship between heart rate and neural activation and to examine the specificity of the relationship between heart rate and neural activation for externally guided versus intentional action control. ROI analyses were performed with the MarsBaR toolbox in SPM8 (Brett, et al., 2002) (http://marsbar.sourceforge.net).

## 4.3 Results

***Behavior***

Participants responded in time to the green marble on 65.02 % (*SD* = 6.79) of the trials, and decided to intentionally inhibit responding to the white marble on 44.99 % (*SD* = 8.38) of the trials.

Participants were substantially slower to respond to the white (*M* = 359, *SD* = 68) compared to the green (*M* = 294, *SD* = 21) marble trials, $F(1, 15) = 21.72$, $p < .001$, indicating that the decision process on the white marble trials took longer.

***Heart Rate***

IBIs were computed separately for the externally guided green go condition and the intentional white go and white nogo conditions. To test for differences in heart rate responses between the three different conditions, a Condition (3: green go, white go, white nogo) x IBI (4: IBI -1 to IBI 2) repeated measures ANOVA was performed. A main effect of IBI was observed, $F(3, 51) = 7.78$, $p < .01$, indicating that heart rate decelerated in anticipation of marble movement (onset during IBI 0), followed by an acceleratory recovery (see Figure 1). A Condition x IBI interaction, $F(6, 102) = 11.13$, $p < .001$, indicated that heart rate responses differed between the different conditions. Follow-up repeated measures ANOVAs on IBI 1 (during which participants decided between acting and inhibiting), showed that heart rate deceleration was less pronounced for the externally guided green go condition compared to both the intentional white go condition, $F(1, 15) = 20.10$, $p < .001$, and the intentional white nogo condition, $F(1, 15) = 25.98$, $p < .001$. Finally, heart rate deceleration was more pronounced for the intentional white nogo compared to the intentional white go condition, $F(1, 15) = 6.37$, $p < .05$.

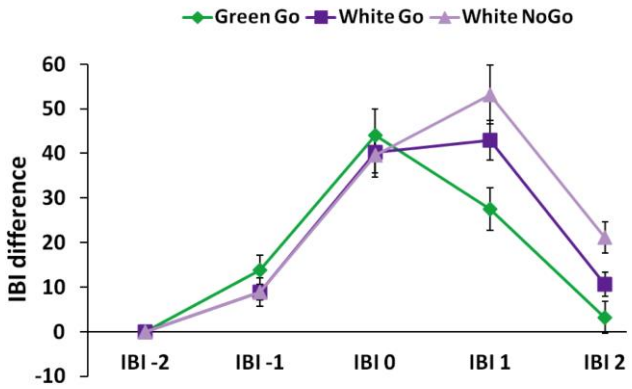


**Figure 1:** Stimulus-locked heart rate changes associated with externally guided action (Green Go), intentional action (White Go) and intentional inhibition (White NoGo). IBI 0 refers to the IBI during which the marble started to roll down the ramp. An increase in IBI difference scores indicates heart rate deceleration, and a decrease in IBI difference scores indicates heart rate acceleration.

### *Heart Rate and fMRI correlations*

In order to examine the relation between heart rate deceleration and neural activation during action control, whole-brain regression analyses with IBI 1 difference scores as regressors were performed on the three conditions (green go, white go and white nogo) versus fixation baseline (null). The reason for focusing on the conditions versus fixation baseline was because condition versus baseline typically has higher reliability and is not contaminated by individual differences in "control condition" responsiveness (see Ordaz, Foran, Velanova, & Luna, 2013).

For externally guided action (the green go condition), average IBI 1 difference scores were added as a regressor to the contrast green go > null. This analysis revealed activation in right lateral prefrontal cortex (lateral PFC) and right paracentral lobe (see Figure 2A and Table 1). A ROI analysis showed that right lateral prefrontal cortex was more active for individuals who showed stronger heart rate deceleration during externally guided action (see Figure 2D).

For intentional action (the white go condition), average IBI 1 difference scores were added as a regressor to the contrast white go > null. This analysis revealed activation in medial frontal cortex and supplementary motor area (SMA) (Figure 2B, see Table 1 for a full list of active areas). A ROI analysis showed that medial frontal cortex was more active for individuals who showed stronger heart rate deceleration during intentional action (see Figure 2H).

Finally, for intentional inhibition (the white nogo condition) average IBI 1 difference scores were added as a regressor to the contrast white nogo > null. This analysis also revealed activation in medial frontal cortex (Figure 2C, see Table 1 for a full list of areas). A ROI analysis showed that medial frontal cortex was more active for individuals who showed stronger heart rate deceleration during intentional inhibition (see Figure 2L).

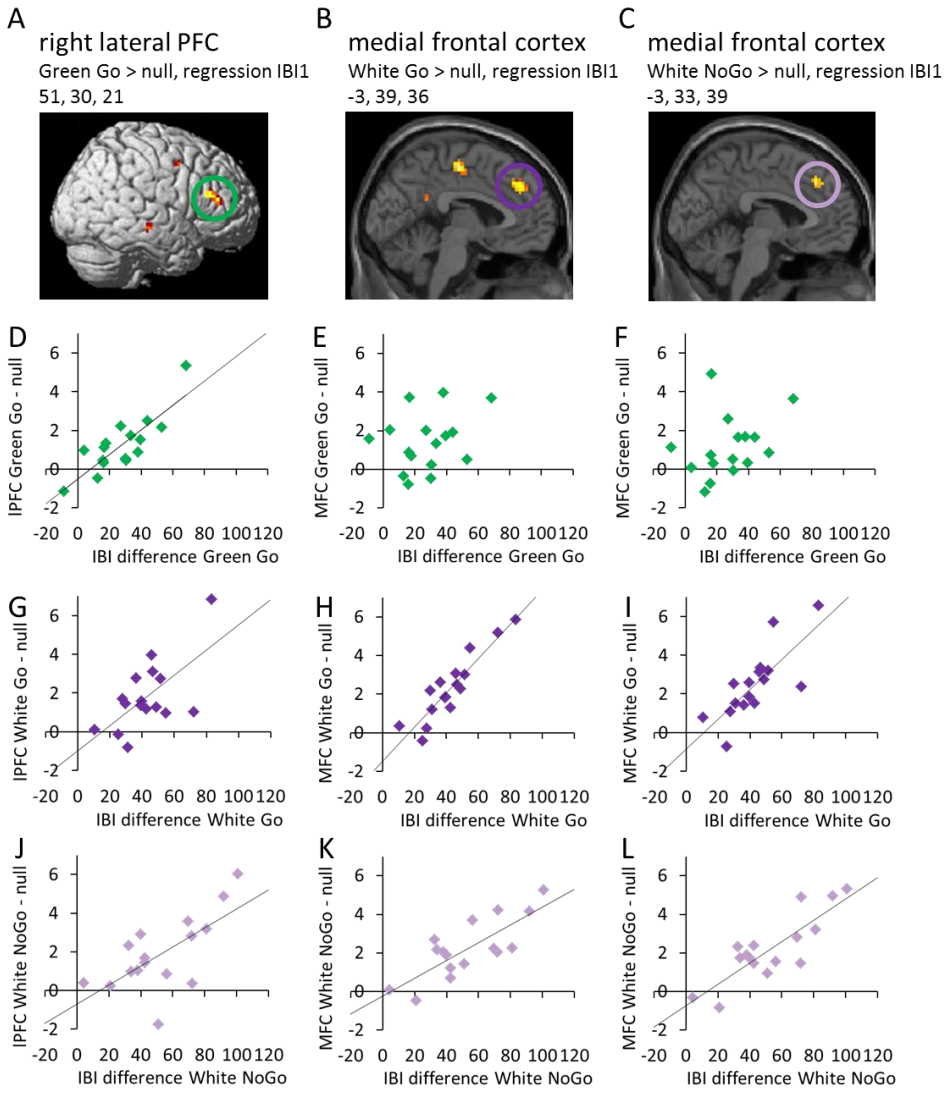


**Figure 2:** Whole brain regression analyses showing relation between heart rate deceleration and neural activation for: **A.** externally guided action (Green Go), **B.** intentional action (White Go) and **C.** intentional inhibition (White NoGo) (uncorrected $p < .001$, at least 10 contiguous voxels). **D-L.** Associations between heart rate deceleration and neural activation for the different task conditions. Trendlines are added for significant correlations.

**Table 1.** Brain regions revealed by whole-brain regression analyses (all $p < .001$ uncorrected, > 10 voxels).

| Anatomical region | L/R | K | Z | MNI coordinates | | |
|---|---|---|---|---|---|---|
| | | | | x | y | z |
| **Green Go > null, regression IBI 1** | | | | | | |
| Paracentral Lobe | r | 14 | 3.88 | 9 | -27 | 63 |
| Lateral PFC (IFG) | r | 28 | 3.83 | 51 | 30 | 21 |
| **White Go > null, regression IBI 1** | | | | | | |
| Supplementary Motor Area | l | 100 | 4.80 | -3 | -18 | 54 |
| Superior Frontal Gyrus | l | 38 | 4.16 | -21 | 21 | 39 |
| Para Hippocampal Area | l | 22 | 4.16 | -15 | -12 | -24 |
| Medial Frontal Cortex (SMG) | l | 40 | 4.15 | -3 | 39 | 36 |
| Anterior Cingulate Cortex | r | 29 | 4.00 | 9 | 36 | 12 |
| Posterior Cingulate Cortex | l | 11 | 3.03 | 0 | -48 | 27 |
| Inferior Parietal Lobe | l | 20 | 3.83 | -48 | -33 | 45 |
| Amygdala | l | 17 | 3.81 | -30 | 3 | -18 |
| Hippocampus | l | 18 | 3.73 | -18 | -24 | -12 |
| Superior Frontal Gyrus | l | 11 | 3.73 | -18 | 54 | 6 |
| Occipital Lobe | l | 13 | 3.66 | -48 | -72 | -9 |
| Supplementary Motor Area | r | 15 | 3.65 | 9 | 24 | 48 |
| Middle Temporal Gyrus | r | 10 | 3.64 | 45 | -36 | 3 |
| Precentral Gyrus | r | 10 | 3.49 | 54 | 3 | 24 |
| **White NoGo > null, regression IBI 1** | | | | | | |
| Amygdala | l | 41 | 4.43 | -30 | 3 | -21 |
| Para Hippocampal Area | r | 42 | 4.41 | 18 | -30 | -12 |
| Occipital Lobe | l | 11 | 4.12 | -15 | -66 | 39 |
| Medial Frontal Cortex (SMG) | l | 34 | 4.03 | -3 | 33 | 39 |
| Inferior Parietal Lobule | l | 30 | 3.95 | -51 | -36 | 42 |
| Superior Temporal Gyrus | r | 10 | 3.67 | 66 | -15 | 12 |

In order to examine the specificity of the relationship between heart rate deceleration and neural activation for externally guided versus intentional action control in lateral and medial prefrontal cortex, we performed additional ROI analyses. For the ROI in right lateral PFC, which was taken from the regression analysis for externally guided action, values for intentional action and intentional inhibition were extracted. Intentional action related activation in this area correlated with IBI 1 difference scores for intentional action ($r = .637$, $p < .01$) (see Figure 2G), and intentional inhibition related activation in this area correlated with IBI difference scores for intentional inhibition ($r = .670$, $p < .01$) (see Figure 2J). For the ROI in medial frontal cortex, which was taken from the regression analysis for intentional action, values for externally guided action and intentional inhibition were extracted. Externally guided action activation in this area did not correlate with IBI 1 difference

scores for externally guided action ($p > .2$) (see Figure 2E), whereas intentional inhibition related activation in this area did correlate with IBI 1 difference scores for intentional inhibition ($r = .778$, $p < .001$) (see Figure 2K). Finally, for the ROI in medial frontal cortex, which was taken from the regression analysis for intentional inhibition, values for externally guided action and intentional action were extracted. Externally guided action activation in this area did not correlate with IBI 1 difference scores for externally guided action ($p > .2$) (see Figure 2F), whereas intentional action related activation in this area did correlate with IBI 1 difference scores for intentional action ($r = .771$, $p < .001$) (see Figure 2I). Taken together, these results show specificity of the relation between heart rate deceleration and neural activation in medial frontal cortex for intentional action control (i.e. both intentional action and intentional inhibition), but not for the relation between heart rate deceleration and neural activation in right lateral PFC for externally guided control.

## 4.4 Discussion

The present study was the first to examine the role of a central autonomic network in intentional and externally guided action control in a combined neuroimaging and heart rate study. In line with our previous heart rate study outside the scanner (Schel, et al., 2013), the heart rate results showed a pronounced heart rate deceleration during both intentional action and inhibition decisions, indicating that heart rate is sensitive to intentional decisions. Furthermore, the results showed that heart rate deceleration during intentional action control was associated with activation in medial frontal cortex, whereas heart rate deceleration during externally guided action control was associated with activation in right lateral PFC. Here we will discuss these findings vis-à-vis recent hypotheses about the functioning of the central autonomic network and the relation between heart rate responses and neural activation.

In this study both intentional and externally guided action control involved activation of a central autonomic network. However, the implementation of this central autonomic network differed between intentional and externally guided action control. On the autonomic level, the results showed that both intentional and externally guided action control are associated with heart rate deceleration. There was however a difference in the level of autonomic responsiveness, such that heart rate deceleration was more pronounced for intentional compared to externally guided action control. On the central level, the results showed that the association between heart rate deceleration and neural responsiveness differed between intentional and externally guided action control, such that for intentional action control the association was observed in medial frontal cortex and for externally guided action control the association was observed in right lateral PFC. These results are in line with previous research suggesting a medial/lateral distinction for intentional versus externally guided action control (Brass & Haggard, 2008; Goldberg, 1985; Krieghoff, et al., 2011). However, the ROI analyses suggest that this distinction is only partial. That is, for externally guided action control heart rate deceleration is associated with activation in right lateral PFC, whereas for intentional action control (both intentional

action and intentional inhibition) heart rate deceleration is associated with activation in medial frontal cortex, but also in right lateral PFC. These results extent previous findings by showing that regions in lateral PFC are also important for intentional action control (Karch, et al., 2009; Orr & Banich, 2014).

The present study was one of the first to examine the relationship between parasympathetic mediated heart rate deceleration and neural activation during a cognitive task. Previous studies examining the relation between parasympathetic mediated heart rate changes and neural activation have mainly looked at physical tests, such as a handgrip exercise (Norton, Luchyshyn, & Kevin Shoemaker, 2013; Wong, Masse, Kimmerly, Menon, & Shoemaker, 2007). These studies have shown ventromedial PFC (vmPFC) to be important in modulating heart rate (Norton, et al., 2013; Wong, et al., 2007). This vmPFC region is more ventral compared to the medial frontal cortex region, which we have found to be associated with heart rate deceleration during intentional action control. Interestingly, this region in medial frontal cortex is close to the midcingulate cortex region found to be associated with sympathetic regulation in a large meta-analysis on the central processing of autonomic function (Beissner, Meissner, Bar, & Napadow, 2013). In contrast, the lateral PFC region, which was associated with heart rate deceleration during externally guided action control, has not been previously implicated in parasympathetic cardiac control. Besides the medial frontal cortex being important in the central autonomic network for intentional action control, the left amygdala was also found to be associated with heart rate deceleration during intentional action control (both intentional action and intentional inhibition). Previous research has found the amygdala to be one of the key regions via which the prefrontal cortex influences heart rate (Thayer & Lane, 2009), both for sympathetic and parasympathetic regulation (Beissner, et al., 2013). However, the left amygdala was not found to be associated with heart rate deceleration during externally guided action control.

Some limitations of the present study deserve mentioning. First, due to scanner artifacts on the heart rate date, the final sample size of the current study was relatively small. Future studies should replicate these findings in a larger sample. Second, our paradigm did not include an externally guided inhibition condition, only externally guided action. It will be an interesting question for future research to examine the role of the central autonomic network in intentional versus externally guided inhibition.

To conclude, the present study examined the role of the central autonomic network in an action control task in a combined heart rate and neuroimaging study. The results of this study demonstrate a relation between autonomic responsiveness and neural activity in key brain regions for action control, and extent the existing literature by showing that heart rate deceleration during action control is an integrated part of the central autonomic network, dissociating between intentional and externally guided action control on a medial to lateral dimension (Krieghoff, et al., 2011).