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SHORT COMMUNICATION

# Midbrain volume predicts fMRI and ERP measures of reward reactivity

**Joshua M. Carlson · Dan Foti · Eddie Harmon-Jones · Greg H. Proudfit**

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**Abstract** Ventral striatal activation measured with functional magnetic resonance imaging (fMRI) and feedback negativity amplitude measured with event-related potentials (ERPs) are each enhanced during reward processing. Recent research has found that these two neural measures of reward processing are also related to one another, such that increases in ventral striatal activity are accompanied by increases in the amplitude of the feedback negativity. Although there is a long history of research implicating the midbrain dopamine system in reward processing, there has been little research into the possibility that structural variability in the midbrain may be linked to functional variability in reward reactivity. Here, we used structural MRI to measure midbrain volumes in addition to fMRI and ERP measures of functional neural reactivity to rewards in a simple gambling task. The results suggest that as midbrain volumes increase, fMRI reward reactivity in the ventral striatum and medial prefrontal cortex also increases. A similar relationship exists between midbrain structure and the amplitude of the feedback negativity; further, this relationship is mediated specifically by activity in the ventral striatum. These data demonstrate convergence between neuroanatomical, hemodynamic, and electrophysiological measures. Thus, structural variability in the midbrain relates to variability in fMRI and ERP measures of functional reward reactivity, which may play a critical role in reward-related psychopathologies and the treatment of these disorders.

**Keywords** Reward · Striatum · Volume · Morphology · Feedback negativity · VBM

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## Introduction

The ability to crave, seek, detect, obtain, and enjoy resources or actions that benefit an organism's survival is an essential aspect of motivated drive states. A long history of neuroscience research in animals has implicated the dopaminergic projections from the midbrain to the ventral striatum (VS) in reward processing (Olds and Milner 1954; Wise 1996). In human functional magnetic resonance imaging (fMRI) studies the VS activates in response to a number rewarding stimuli such as drugs (Breiter et al. 1997; Drevets et al. 2001), erotic images (Walter et al. 2008; Sabatinelli et al. 2007), pleasant tastes (O'Doherty et al. 2002), attractive faces (Senior 2003), monetary rewards (Knutson and Bossaerts 2007), and favorable social interactions (Zink et al. 2008). Additional evidence using event-related potentials (ERPs) has identified the "feedback negativity" (FN; 300 ms) as an evoked potential that is sensitive to rewarding versus non-rewarding stimuli (Gehring and Willoughby 2002; Miltner et al. 1997; Holroyd et al. 2008; Foti et al. 2011). The amplitude of the FN is thought to track the relative valence of outcomes

(Holroyd et al. 2006, 2004). Recent research has explored the relationship between fMRI and EEG measures of reward anticipation (Plichta et al. 2013) and reward feedback (Carlson et al. 2011). In particular, research by our group demonstrates that increased VS activity is linked to increased FN amplitude (Carlson et al. 2011).

Ventral Striatal activity (Wise 1996) and FN amplitude (Holroyd and Coles 2002) are both thought to be influenced by the dopaminergic midbrain. Yet, the extent to which structural variability in midbrain morphology relates to variability in these measures of neural reactivity remains unknown. The importance of establishing the relationship between brain structure and reward reactivity is highlighted by research linking blunted reward processing to depressive symptoms. Indeed, both blunted VS activity (Epstein et al. 2006; Fitzgerald et al. 2008; Pizzagalli et al. 2009) and FN amplitude (Foti and Hajcak 2009) to rewards have been linked to heightened levels of depression. In addition, research suggests that a blunted FN amplitude is associated with depression as early as late childhood (Bress et al. 2012, 2013b) and a blunted FN prospectively predicts the onset of a major depressive episode (Bress et al. 2013a). The symptom of anhedonia in particular has been linked to blunted VS reward reactivity (Keedwell et al. 2005; Wacker et al. 2009) and deep brain stimulation of the VS attenuates the symptoms of anhedonia in depressed individuals (Schlaepfer et al. 2008). It is possible that these individual differences in reward reactivity may be driven in part by structural differences in midbrain morphology. Thus, given the importance of reward processing in normative adaptive behavior and depressive behavior, it is essential to understand the structure–function relationship of reward processing in the brain.

The focus of the current study was to link functional measures of reward processing as measured by fMRI and ERP (i.e., VS activation and FN amplitude, respectively) to underlying variability in neural structure within the dopaminergic midbrain as measured by structural MRI. Participants completed a gambling task, which contained equal numbers of trials containing monetary wins and losses in both fMRI and ERP environments (Foti and Hajcak 2009; Hajcak et al. 2006). Given the longstanding association between midbrain-regulated dopaminergic neurotransmission and reward processing, we predicted that the magnitude of reward-related reactivity in the VS and FN across individuals would positively correlate with variability in midbrain volume.

## Methods

### Participants

The same sample of 45 (Male = 27) consenting adults between the ages of 19 and 25 ($M = 21.11$, $SD = 1.27$) that participated in our previously published study (Carlson et al. 2011) assessing correlations between fMRI and ERP measures was also used for the current manuscript. Participants were screened for metal and were monetarily compensated for their time. The Institutional Review Board of Stony Brook University approved this study.

### Gambling task

The details of the experimental task as well as the fMRI and EEG preprocessing and analysis procedures have previously been described in detail (Carlson et al. 2011). Functional MRI and EEG data were collected in separate counterbalanced sessions, while participants performed a simple gambling task. Briefly, trials began with a white fixation cue presented in the center of a black screen. After which, a screen displayed two doors side-by-side and participants were instructed to choose a door. Behind one of the doors there was a monetary prize (+$0.50), while behind the other door there was a loss (−$0.25). After another brief fixation cue, a feedback screen was displayed where a green '↑' indicated a win, and a red '↓' indicated a loss. The task consisted of 60 trials with 30 predetermined wins and losses presented in a pseudorandom order.

### EEG and fMRI measures

*Win* > *Loss* VS activity and FN amplitude data were used in a previous report (Carlson et al. 2011). Here, we utilized the same extracted BOLD data from the left and right VS as well as the medial prefrontal cortex (mPFC; left hemisphere maxima extending bilaterally). In addition, *Win* > *Loss ERP* activity corresponding to the FN was extracted using temporal-spatial principal components analysis ($FN_{PCA}$). The details regarding these measures can be obtained in our earlier report (Carlson et al. 2011). As previously reported, the $FN_{PCA}$ correlated with the VS (left: $r = 0.28$, $p < 0.05$ and right: $r = 0.52$, $p < 0.001$) and mPFC ($r = 0.26$, $p < 0.05$) as well as other reward-related regions (Carlson et al. 2011).

### Structural image acquisition and analysis

A 3 Tesla Siemens Trio whole body scanner was used to acquire $T_1$ images with the following parameters: TR = 1,900 ms, TE = 2.53, flip angle = 9°, FOV = 176 × 250 × 250 mm, matrix = 176 × 256 × 256, and voxel size = 1 × 0.98 × 0.98 mm.

We used voxel-based morphology (VBM) as an automated user-independent voxel-wise measurement of the associations between regional brain volumes and individual differences in reward reactivity. The VBM approach has been extensively cross-validated with manual

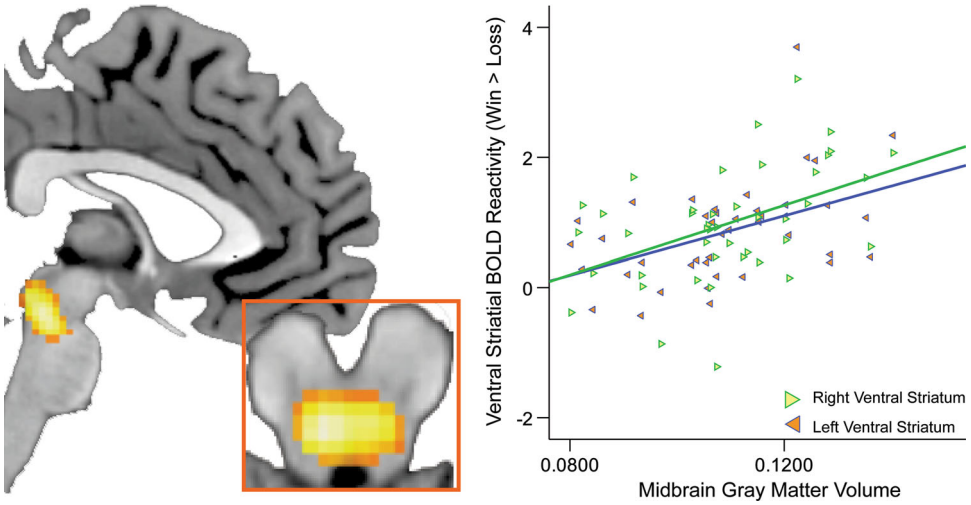


**Fig. 1** Results of a whole-brain analysis reveal a cluster of voxels correlating with right ventral striatal activation to monetary rewards relative to losses within the midbrain which appears to encompass portions of the periaqueductal gray and ventral tegmental area (*left*). Scatterplot of extracted midbrain gray matter volume and functional win > loss reactivity from fMRI task indicates that for both the left and right ventral striatum as midbrain volume increases, ventral striatal activation increases (*right*). These correlations remain significant when potential outliers with the highest ventral striatal BOLD reactivity are excluded (*left* $r = 0.27$, $p < 0.05$ and *right* $r = 0.58$, $p < 0.001$)

volumetric analysis (Woermann et al. 1999). The technique derives volume measurements from transformation of individual structural MR volume images into a common stereotactic space, which allows the testing of differences in sub-volumes of distinct brain regions using general linear model statistics. The VBM methodology used in this report is similar to the procedures described previously (Ashburner and Friston 2000). First, we manually adjusted volume brain images to a common orientation (origin at the anterior commissure) before all images were pre-processed using standard VBM procedures in SPM8 (http://www.fil.ion.ucl.ac.uk/spm). We visually examined the $T_1$-weighted MPRAGE images for artifacts and structural abnormalities. We then segmented these images into gray matter, white matter and cerebrospinal fluid, after which they were again visually inspected. Gray and white matter images were normalized to standard gray matter templates in SPM8 (Ashburner and Friston 2000). Lastly, tissue probability maps were obtained by averaging across participant data, using an 8-mm FWHM Gaussian smoothing kernel. Measures of total gray matter volume were obtained from summed global signal of segmented images of gray matter.

In our earlier study, right ventral striatal activation was both the global maxima from the fMRI analysis and the best predictor of FN amplitude (Carlson et al. 2011). Therefore, participant's extracted right ventral striatal BOLD activity was used as a predictor variable with gray matter volume as the dependent variable using multiple regression within SPM8. We specifically tested whether or not increased gray matter volume would correlate with greater BOLD activity. Age and whole-brain gray matter volume were included as covariates to control for their potentially confounding effects on regional gray matter (Ge et al. 2002). An initial whole-brain threshold was set to $P_{\text{single-tailed}} < 0.001$ and a whole-brain cluster-level family-wise error correction (FWE) was applied. Follow-up partial correlations (controlling for age and whole-brain gray matter) were performed on gray matter volume extracted from a region in the midbrain identified in the SPM8 regression.

## Results

As can be seen in Fig. 1, a cluster of voxels extending bilaterally within the midbrain of the brainstem, which appears to encompass portions of the periaqueductal gray and ventral tegmental area, correlated with participant's right ventral striatal BOLD activity, $k = 165$, peak voxel at $-4, -28, -16$; $t_{38} = 5.05$, $P_{\text{FWE-corrected}} < 0.05$. No other regions correlated with right ventral striatal BOLD activity. We then performed additional partial correlations (controlling for age and whole-brain gray matter) on gray matter values extracted from the midbrain cluster identified in the SPM analyses. These follow-up analyses indicate that the association between gray matter volume and BOLD activity is present for both the left ($r = 0.32$, $P_{\text{one-tailed}} = 0.02$) and the right ($r = 0.59$, $P_{\text{one-tailed}} = 0.00003$) ventral striatum as well as the mPFC ($r = 0.38$, $P_{\text{one-tailed}} = 0.007$). In addition, midbrain gray matter volume correlated with

$FN_{PCA}$ amplitude, $r = 0.30$, $P_{\text{one-tailed}} = 0.03$ (partial correlation controlling for age and whole-brain gray matter).

Given that $FN_{PCA}$ amplitude has been linked to underlying VS and mPFC activation (Carlson et al. 2011), we then ran a mediation analysis to test whether the association between $FN_{PCA}$ amplitude and midbrain gray matter was accounted for by functional activation in the right VS and mPFC. Controlling for age and whole-brain gray matter, midbrain gray matter significantly predicted functional right VS activation ($\beta = 0.73$, $P_{\text{one-tailed}} = 0.00003$). When both midbrain gray matter and functional VS activation were added as simultaneous predictors of $FN_{PCA}$ amplitude, right VS activation continued to predict $FN_{PCA}$ amplitude ($\beta = 0.62$, $P_{\text{one-tailed}} = 0.0003$), but midbrain gray matter did not ($\beta = -0.08$, $P_{\text{one-tailed}} = 0.34$). The Sobel test revealed that this mediation effect was statistically significant ($z = 2.91$, $P_{\text{one-tailed}} = 0.002$), indicating that the association between midbrain gray matter and $FN_{PCA}$ amplitude was fully mediated by functional VS activation.

By contrast, mPFC activation did not mediate the relationship between midbrain gray matter and $FN_{PCA}$ amplitude. Controlling for age and whole-brain gray matter, midbrain gray matter significantly predicted functional mPFC activation ($\beta = 0.48$, $P_{\text{one-tailed}} = 0.007$). When both midbrain gray matter and functional mPFC activation were added as simultaneous predictors of FN amplitude, however, neither association was significant (midbrain: $\beta = 0.28$, $P_{\text{one-tailed}} = 0.09$; mPFC: $\beta = 0.17$, $P_{\text{one-tailed}} = 0.16$); the Sobel test yielded no significant effect of mediation ($z = 0.95$, $P_{\text{one-tailed}} = 0.17$).

## Discussion

We found that as midbrain volumes increased, fMRI reward reactivity in the VS and mPFC also increased. In addition, increases in midbrain volume were associated with an increased FN amplitude to reward. The association between midbrain volume and FN amplitude was mediated by VS reward reactivity. On the other hand, the relationship between midbrain volume and FN amplitude was not mediated by mPFC reward reactivity.

Gray matter volume is thought to represent the density of neuronal and glial cell bodies in addition to the number of dendritic branches and short range axons (Zatorre et al. 2012). Therefore, gray matter volume can be thought as a measure of local network integrity. Although the exact functional significance of this local network integrity remains unclear, presumably greater integrity in dopamine-producing neurons in the midbrain should coincide with greater dopamine production and availability in target regions such as the VS and mPFC. It has been proposed that dysfunction specifically in the midbrain-VS circuit may be a primary etiological factor in depression (Nestler and Carlezon 2006; Russo and Nestler 2013). Indeed, recent animal data indicate that phasic dysregulation of midbrain neurons projecting to the VS—but not the mPFC—mediates depressive behavior under conditions of environmental stress (Chaudhury et al. 2013). In humans, depression is associated with lower midbrain volumes (Lee et al. 2011). Based on the present data, this structural abnormality in the midbrain may relate to functional abnormalities in depression—particularly blunted VS reactivity (Keedwell et al. 2005; Wacker et al. 2009) and FN amplitude (Bress et al. 2013a, b, 2012; Foti et al. 2011) to reward. Similarly, blunted VS activity to reward in other patient populations such as attention deficit hyperactivity disorder (Plichta and Scheres 2013) may also be linked to lower midbrain volumes. On the other end of the spectrum, greater midbrain volume may be related to over activation of the VS-mPFC reward circuit and the corresponding hypersensitivity to reward observed in pathological gamblers. Pathological gamblers have been shown to have increased midbrain activity to near miss losses in a slot machine gambling task and activation of the midbrain in these individuals correlates with activity in the VS (Habib and Dixon 2010). Based on the current results, we would expect this hypersensitivity to reward to be driven by enlarged midbrain volumes. Future research should test this possibility directly by examining changes in the structure–function relationship of reward processing within various patient populations along the reward sensitivity spectrum.

It should be noted that it is unclear from the current results as to whether lower midbrain volumes are a risk factor for blunted reward or rather a consequence of this behavior. The predominant theory for reduced gray matter volumes in depression claims that such reductions are linked to stress-mediated cell death by glucocorticoids (Woolley et al. 1990; Sheline et al. 2002). Although this mechanism has particularly been linked to reduced hippocampal and medial prefrontal cortical volumes (Bora et al. 2012; Kempton et al. 2011), it could also explain reduced midbrain gray matter in those with blunted reactivity to reward. On the other hand, decreased reactivity to reward may, over time, result in lower levels of gray matter within the dopaminergic midbrain diffuse modulatory centers. That is, it is unclear within our sample as to whether reduced gray matter within the midbrain is the cause or the effect of blunted reward reactivity. In either case, midbrain gray volumes are closely linked to current levels of reward reactivity.

Recent research has shown that learning a new skill or training results in neuroplasticity, which is observable in the MRI signal (Zatorre et al. 2012). It has recently been suggested that tracking gray matter changes related to treatments of anxiety disorders such as attention bias

modification may be useful in assessing the efficacy of such treatments (Carlson et al. 2013). That is, the relative success of treatment in reducing one's attentional bias to threat and level of anxiety should correspond to the degree of structural change within a particular brain network (i.e., the amygdala—anterior cingulate network for attention bias (Carlson et al. 2012, 2013). Similarly, given the association between functional reward reactivity and midbrain gray matter volume observed here and the link between functional reward reactivity and symptoms of anhedonia (Keedwell et al. 2005; Wacker et al. 2009), the efficacy of treatments aimed at alleviating this symptom may be linked to structural changes within the midbrain as well as functional measures of reward reactivity. Future research should assess the extent to which successful treatment results in structural changes within the midbrain and the degree to which these potential changes are reflected in functional measures such as the FN. If structural change is predictive of treatment outcome and can be tracked through the FN, this would allow for easier implementation of tracking treatment status through physiological measures as EEG is considerably less expensive than MRI.

In sum, variability in midbrain gray matter volume accounts for variability in VS reactivity and FN amplitude to rewards. Structural abnormalities in the midbrain may underlie reward-related psychopathologies and the treatment of these disorders.

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