SUPPLEMENTARY INFORMATION

METHODS

FDOPA measures: Twenty-one participants (mean age 31, 6 females) completed

positron emission tomography (PET) scanning. In a single PET session, two sixty-

second, 12 mCi $[^{15}O]H_2O$ rCBF emission scans, and a 90-minute series of dynamic 16-

$[mCi]^{18}F$-DOPA emission scans were obtained after oral administration of carbidopa to

prevent peripheral radiotracer degradation. Using a voxel-wise Patlak method with a

cerebellar reference region, FDOPA Ki, reflecting presynaptic dopamine (DA) stores and

synthesis, was determined for every voxel in the brain. After a midbrain volume of

interest was hand drawn on native-space MRI images, each individual's structural MRI

scan was then co-registered to the native-space FDOPA Ki images (using SPM99) in

order to extract average midbrain Ki values (Supplementary Figure 1). These Ki values

have been shown to be stable over time[1] suggesting that they represent stable state (trait)

measures of presynaptic DA synthesis.[1]

Stimuli and Functional imaging: The same 21 FDOPA PET participants underwent

event-related fMRI to measure BOLD using a GE 3T scanner with a 16 channel Nova

head coil, TR = 2.210s, TE = 25, FOV = 20, Flip Angle = 90) while they viewed 10 1-

second videos for each emotional (fear and happy) and neutral facial expression[2] during a

randomized slow event-related (stimuli jittered 4-16s ISI) functional magnetic resonance

imaging (fMRI) with each stimulus being shown twice. Movement of facial muscles in

the videos was assessed using the freely available PerceptualDiff image comparison

utility that compares each frame with the previous one (http://pdiff.sourceforge.net).

Averages of these differential movement parameters for all the videos in each emotional category were measured across time, representing global face and head movement (Figure 1**D & E**).

In addition to this objective assessment of global facial movement, we recruited 12 individuals (mean age = 24 years, 6 females) who were trained to manually scroll (using their dominant right hand) through each of the 10 videos in each emotional category frame by frame (1-30 frames in total for the 1 second videos) using Adobe Premier (a video processing software) to indicate which frame portrayed the first emergence of fear or happiness. Each indicated frame number for each video was taken as the point of emerging (salient) fear or happiness for that individual rating. These ratings were converted from frame numbers to milliseconds and the Mean ±SEM of these ratings of emergence of salient fear and happiness were calculated (Fear = 757.42ms ±14.27 and Happy = 709.93ms ±45.14).

Preprocessing, including coregistration of functional scans into each participants' anatomical *ASSET MPRAGE* MRI scan (FOV = 20, TE = Min Full, Flip Angle = 6), followed by first and second level RFX analysis was done using statistical parametric mapping version 5 (SPM5) (http://www.fil.ion.ucl.ac.uk/spm/software/spm5). In order to better capture the temporal dynamics of the DA-modulated neural response, 16 of the 21 fMRI participants (mean age=34.2; 4 females) repeated the same paradigm during MEG. Participants viewed single presentations of the 10 dynamic fear, happy and neutral facial expression videos in a randomized event-related design (stimuli jittered with 2-6s ISI). Second-level analyses for both fMRI and MEG were performed using midbrain Ki values as predictors of BOLD and MEG signal response in SPM5 and analysis of functional

images (AFNI) software (http://afni.nimh.nih.gov/afni), respectively.

For the MEG data, we focused on low and high gamma frequency oscillations (30-50Hz, and 60-140Hz respectively) given their roles in emotional processing[4] and routing cortical information flow as well as attentional tuning.[5] Each scan was acquired using a whole-head array of 275 radial first order gradiometer/SQUID channels[6] with the CTF system. The images were coregistered onto structural MRI scans in 3d space (Supplementary Figure 2) using synthetic aperture magnetometry (SAM)[7] beamformer method combined with AFNI. A linearly constrained minimum variance beamformer method for estimation of source activity representing changes in power at each latency as determined by time frequency transform for each voxel of the brain[6,7] was applied (Supplementary Figure 2). Source analysis guided estimation of whole brain local neural activity as a function of time and oscillatory frequency.[7] MEG timecourse data representing MEG signal values were extracted using SAMtime by raw z-scores within gamma frequency bands.

For visualization of the results, ASSET structural MPRAGES were anatomically normalized with DARTEL[3] and then averaged separately for the 21 fMRI participants and the subset of 16 MEG participants. Data are reported at $p < 0.001$, uncorrected.

SUMMARY
Successful processing of motivational signals is critical for survival in a complex environment.[8] Our findings of temporal coincidence of the emergence of the emotional salience of facial expressions on the one hand, and the time windows within which measures of presynaptic midbrain dopamine synthesis predicted transient distributed neural response to the fearful and happy facial expressions[9] on the other, support a role

for the midbrain dopamine system in tuning the spatiotemporal gamma oscillatory coding of emotional salience.[10-13] These results are also in line with findings showing an inhibitory dopaminergic involvement in aversive (fear) as opposed to excitatory involvement in rewarding (happy) experiences[8]. These results may provide the basis for a clinically-and pharmacologically-relevant biomarker of perturbations in midbrain dopamine mediation of gamma oscillatory responses[10,12-15] to emotional salience in neuropsychiatric disorders[9,14,15] that are accompanied by prevalent impairments in emotion cognition.[13-16]
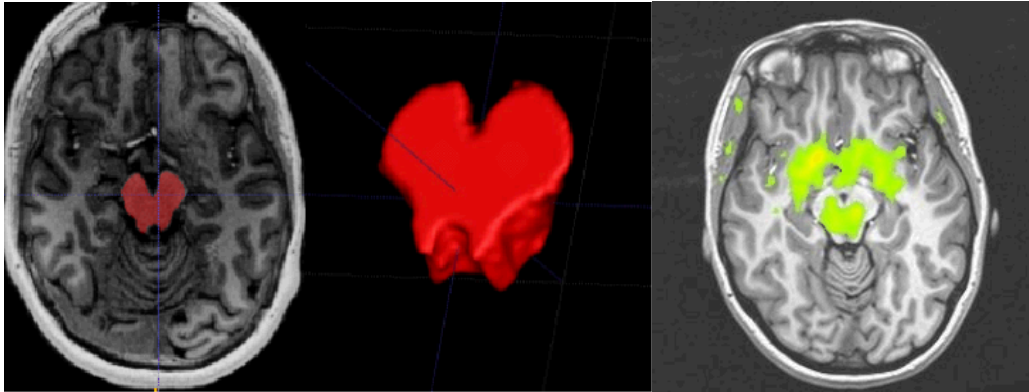
Supplementary Figure 1. Manually segmented midbrain region of interest (ROI), consisting of 12 axial slices drawn on each individual's native space MRI and a 3-dimensional image of the midbrain ROI. The image on the right shows voxel-wise FDOPA uptake coregistered in native MRI space. For each individual, FDOPA Ki values were extracted from the manually segmented midbrain ROI, and these values were used at the second level to predict sustained BOLD response measured with fMRI, and transient gamma oscillatory response with MEG.
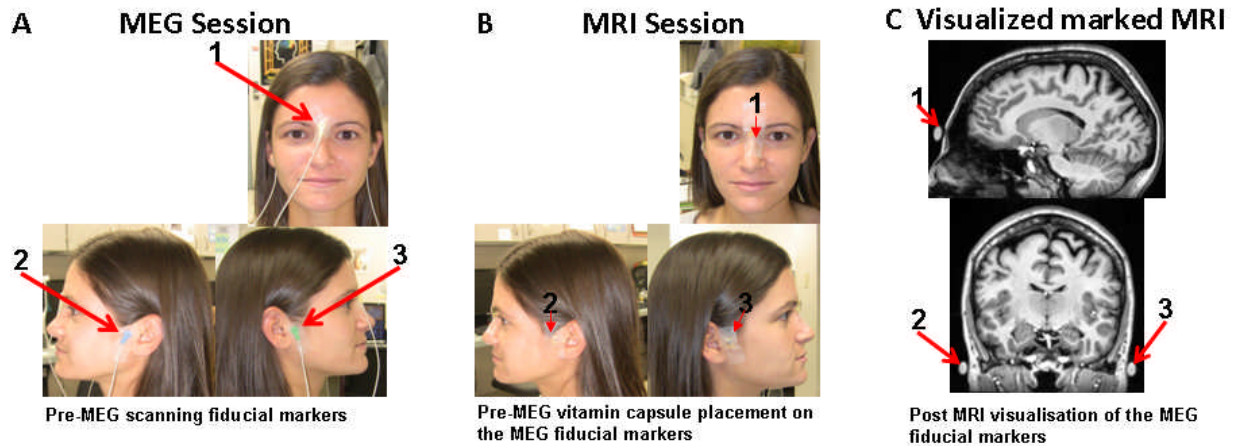
Supplementary Figure 2. Co-registration of MRI and MEG data. **A**, Fiducial points were marked at the nasion (1), and left (2), and right (3) preauricular points before the MEG scan. Pictures of these markers were taken and referenced on the MRI scan exemplified in **B**. Head localization cables were attached at the locations of the fiducial points using adhesive washers. **B**, Structural MRI session showing placement of vitamin E capsules, taped to the head in the same locations as the fiducial points marked during the MEG session. **C**, a T1-weighted MPRAGE was collected and vitamin E capsule locations were visualized and marked using an AFNI toolbox for the purpose of coregistering the MRI and MEG data using the fiducial points marked by the head localization cables in **A**, and vitamin E capsules placed in **B** and visualized in **C**.

SUPPLEMENTARY REFERENCES

1. Vingerhoets FJ, Snow BJ, Schulzer M, Morrison S, Ruth TJ, Holden JE, Cooper S *et al*. *J Nucl Med*. 1994; **35**:18-24.

2. van der Gaag C, Minderaa RB, Keysers C. *Soc Neurosci*. **2,** 179 (2007).

3. Ashburner J. Neuroimage. 2007; **38**(1):95-113.

4. Luo Q, Mitchell D, Cheng X, Mondillo K, Mccaffrey D, Holroyd T *et al*. *Cereb Cortex* 2009; **19**:1896-904.

5. Fries P. *Annu Rev Neurosci* 2009; **32**:209-24.

6. Fife AA, Vrba J, Haid G, Hoang T, Kubik PR, Lee S et al. *Proceedings of the 13th annual conference on biomagnetism* 2002.

7. Robinson SE, Vrba J. 1999 - Sendai, Japan: Tohoku Univ Press.

8. Schultz W, *Annu Rev Neurosci.* **30**, 259 (2007).

9. Haxby JV, Hoffman EA, Gobbini MI. *Trends Cogn Sci.* **4**, 223 (2000).

10. Laviolette SR. *Schizophr Bull* 2007; **33**:971-81.

11. Uhlhaas PJ, Singer W. *Nat Rev Neurosci* 2010; **11**:100-13.

12. Howes O, Bose S, Turkheimer F, Valli I, Egerton A, Stahl D *et al. Mol Psychiatry* 2011, in press.

13. Herrmann CS, Demiralp T. Clin Neurophysiol. 2005; **116**(12):2719-33.

14. Lisman JE et al. Trends Neurosci. 2008; **31**(5):234-42.

15. Lodge DJ, Behrens MM, Grace AA. J Neurosci. 2009; **29**(8):2344-54.

16. Dzirasa K et al. J Neurosci. 2011; **31**(17):6449-56.