

Anatomically distinct dopamine release during anticipation and experience of peak emotion to music

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Music, an abstract stimulus, can arouse feelings of euphoria and craving, similar to tangible rewards that involve the striatal dopaminergic system. Using the neurochemical specificity of [¹¹C]raclopride positron emission tomography scanning, combined with psychophysiological measures of autonomic nervous system activity, we found endogenous dopamine release in the striatum at peak emotional arousal during music listening. To examine the time course of dopamine release, we used functional magnetic resonance imaging with the same stimuli and listeners, and found a functional dissociation: the caudate was more involved during the anticipation and the nucleus accumbens was more involved during the experience of peak emotional responses to music. These results indicate that intense pleasure in response to music can lead to dopamine release in the striatal system. Notably, the anticipation of an abstract reward can result in dopamine release in an anatomical pathway distinct from that associated with the peak pleasure itself. Our results help to explain why music is of such high value across all human societies.

Humans experience intense pleasure to certain stimuli, such as food, psychoactive drugs and money; these rewards are largely mediated by dopaminergic activity in the mesolimbic system, which has been implicated in reinforcement and motivation (see ref. 1 for a review). These rewarding stimuli are either biological reinforcers that are necessary for survival, synthetic chemicals that directly promote dopaminergic neurotransmission, or tangible items that are secondary rewards. However, humans have the ability to obtain pleasure from more abstract stimuli, such as music and art, which are not directly essential for survival and cannot be considered to be secondary or conditioned reinforcers. These stimuli have persisted through cultures and generations and are pre-eminent in most people's lives. Notably, the experience of pleasure to these abstract stimuli is highly specific to cultural and personal preferences, which can vary tremendously across individuals.

Most people agree that music is an especially potent pleasurable stimulus² that is frequently used to affect emotional states. It has been empirically demonstrated that music can effectively elicit highly pleasurable emotional responses^{3,4} and previous neuroimaging studies have implicated emotion and reward circuits of the brain during pleasurable music listening⁵⁻⁸, particularly the ventral striatum⁵⁻⁷, suggesting the possible involvement of dopaminergic mechanisms⁹. However, the role of dopamine has never been directly tested. We used ligand-based positron emission tomography (PET) scanning to estimate dopamine release specifically in the striatum on the basis of the competition between endogenous dopamine and [¹¹C]raclopride for binding to dopamine D₂ receptors¹⁰. Pleasure is a subjective phenomenon that is difficult to assess objectively. However, physiological changes occur during moments of extreme pleasure, which can be used to index pleasurable states in response to music. We used the 'chills' or 'musical frisson'¹¹ response, a well-established marker of

peak emotional responses to music^{5,12-14}. Chills involve a clear and discrete pattern of autonomic nervous system (ANS) arousal¹⁵, which allows for objective verification through psychophysiological measurements. Thus, the chills response can be used to objectively index pleasure, a subjective phenomenon that would otherwise be difficult to operationalize, and allows us to pinpoint the precise time of maximal pleasure.

Previous studies have typically used experimenter-selected musical stimuli⁶⁻⁸. However, musical preferences are highly individualized; thus, to ensure maximal emotional responses, participants were asked to select their own highly pleasurable music. After extensive screening (Online Methods), we recruited a group of people who consistently experienced objectively verifiable chills during their peak emotional responses so that we could quantify both the occurrence and the timing of the most intense pleasurable responses. We also collected psychophysiological measurements (heart rate, respiration rate, electrodermal skin conductance, blood volume pulse amplitude and peripheral temperature) during the PET scans to verify ANS differences between conditions. To account for psychoacoustical differences across self-selected stimuli, we matched musical excerpts using a previously established procedure⁵, such that participants listened to one another's choices, which served as either pleasurable or neutral stimuli. We predicted that if the rewarding aspects of music listening are mediated by dopamine, substantial [¹¹C]raclopride binding potential differences would be found between neutral and pleasurable conditions in mesolimbic regions.

The second aim of our study was to explore the temporal dynamics of any dopaminergic activity, as distinct anatomical circuits are thought to underlie specific phases of reward responses^{16,17}. That is, if there is dopamine release, we wanted to examine whether it is associated with the experience of the reward or with its anticipation¹⁸. Music provides

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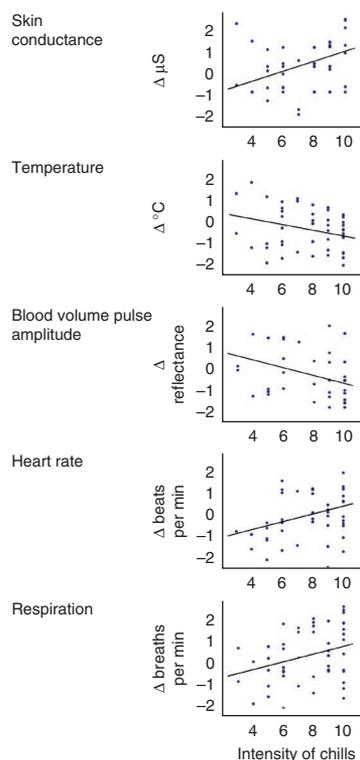
Figure 1 Positive correlation between emotional arousal and intensity of chills during PET scanning. The mean intensity of chills reported by each participant during the PET scanning session was significantly correlated with psychophysiological measurements that were also acquired during the scan. These are indicative of increased sympathetic nervous system activity, suggesting that the intensity of chills is a good marker of peak emotional arousal (**Supplementary Table 1**). The y axis represents standardized z scores for each biosignal. See main text for *P*-values.

an innovative means of assessing this distinction because the temporal unveiling of tonal arrangements elicits anticipatory responses that are based on cognitive expectations and prediction cues^{11,19,20}. These can be examined to isolate the functional components that precede peak pleasurable responses. As PET does not afford the temporal resolution required to examine this distinction, we combined the temporal specificity of functional magnetic resonance imaging (fMRI) with the neurochemical specificity of PET. We acquired fMRI scans with the same participants and stimuli to examine the temporal profile of blood oxygenation level-(BOLD) response specifically in those regions that also showed dopamine release with PET. Striatal dopamine release and BOLD responses are known to be correlated, although the relationship is complex^{9,21}. We predicted that regions revealing dopamine activity in the PET data would show the largest increases in hemodynamic response during peak emotional experiences. We separately analyzed the BOLD data from epochs of peak pleasure and the time immediately preceding these responses (that is, anticipation), based on participants' real-time behavioral responses of when chills were experienced. Spatial conjunction analyses were used to confine the analysis to those striatal voxels showing both dopamine release from PET and increased BOLD during fMRI, which ensured that we were measuring the hemodynamic signal only from regions known to release dopamine in response to the same stimuli. This multimodal procedure revealed a temporally mediated distinction in dopamine release to anticipatory and consummatory responses in the dorsal and ventral striatum, respectively.

RESULTS

PET data: dopamine release and emotional arousal

PET scanning took place over two sessions. Participants listened to either pleasurable music or neutral music during the entire session while both subjective and objective indicators of emotional arousal were collected. Subjective responses from rating scales included self-reports of number of chills, intensity of chills and degree of pleasure



experienced from each excerpt. The mean number of chills for each pleasurable music excerpt was 3.7 (s.d. = 2.8). A paired-samples *t* test confirmed that greater pleasure was experienced during the pleasurable music condition over the neutral music condition ($t(49) = 25.0$, $P < 0.001$). Notably, there was a significant positive correlation between the reported intensity of chills and the reported degree of pleasure ($r = 0.71$, $P < 0.001$), suggesting that the chills response is a good representation of pleasure experienced amongst this group.

Objective measures of psychophysiological signals indicative of emotional arousal collected during the two PET scanning sessions showed significantly higher ANS activity during the pleasurable music condition in all of the variables that we measured: namely, increases in heart rate ($P < 0.05$), respiration ($P < 0.001$) and electrodermal response ($P < 0.05$), and decreases in temperature ($P < 0.01$) and blood volume pulse amplitude ($P < 0.001$; for values, see **Supplementary Table 1**). Subjective

reports of the intensity of the chills response collected via rating scales during PET scanning were significantly correlated with the degree of ANS arousal on all measures: increases in heart rate ($P < 0.05$), respiration ($P < 0.05$) and electrodermal response ($P < 0.01$), and decreases

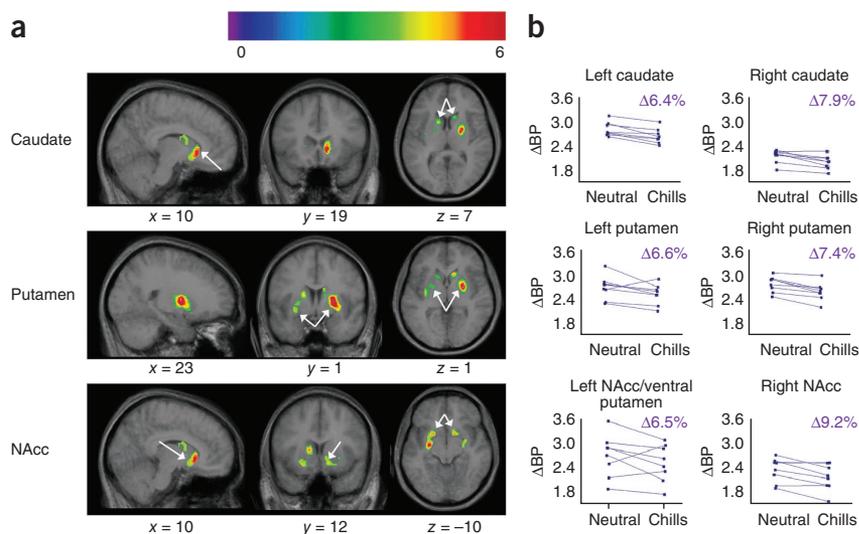
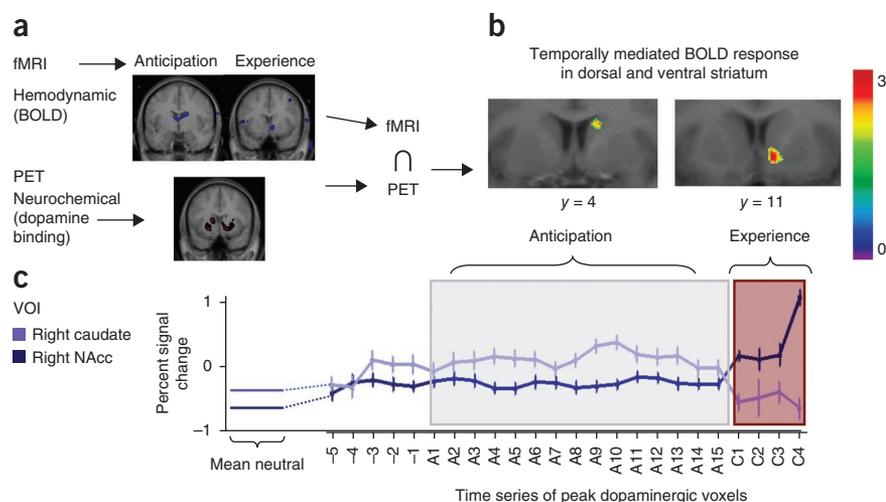


Figure 2 Evidence for dopamine release during pleasurable music listening. **(a)** Statistical parametric maps (*t* statistic on sagittal, coronal and axial slices) reveal significant ($P < 0.001$) [¹¹C]raclopride binding potential (BP) decreases bilaterally in the caudate, putamen and NAcc (white arrows) during pleasurable compared with neutral music listening (**Supplementary Table 2**), indicating increased dopamine release during pleasurable music. **(b)** Changes in binding potential (BP) values plotted separately for each individual; note that the change was consistent for the majority of people at each site.

Figure 3 Combined fMRI and PET results reveal temporal distinctions in regions showing dopamine release. (a) [^{11}C]raclopride PET scan results were spatially conjoined with the fMRI results by creating a mask of significant dopamine release overlaid on BOLD response t maps during each condition. (b) Hemodynamic responses and dopamine activity were maximal in the caudate during anticipatory phases, but shifted more ventrally to NAcc during peak emotional responses. (c) Percent signal change in BOLD response relative to the mean was calculated from the peak voxel of the caudate and NAcc clusters based on the [^{11}C]raclopride PET data. Voxels showing maximum dopamine release in the caudate and NAcc (**Supplementary Table 2**) were identified and percent BOLD signal change was calculated during the fMRI epochs associated with peak emotional responses; values were interpolated for each second preceding this response for each individual, up to 15 s, which was defined as the anticipatory period based on previous findings¹⁵ (see Online Methods for additional details). We found increased activity during anticipation (A1-A15) and decreased activity during peak emotional response (C1-C4) for the caudate, but a continuous increase in activity in NAcc with a maximum during peak emotional responses. The mean signal for neutral epochs for the NAcc and caudate clusters are also plotted for reference, as are the 5 s preceding the anticipation epochs.



in temperature ($P < 0.05$) and blood volume pulse amplitude ($P < 0.05$; **Fig. 1** and **Supplementary Table 1**). This finding further verified that the chills response is a good objective representation of peak emotional arousal in this group.

Analysis of PET data (**Supplementary Methods**) revealed increased endogenous dopamine transmission, as indexed by decreases in [^{11}C]raclopride binding potential, bilaterally in both the dorsal and ventral striatum ($P < 0.001$; **Fig. 2a**) when contrasting the pleasurable music with the neutral music condition. The percentage of dopamine binding potential change was highest in the right caudate and the right nucleus accumbens (NAcc; **Fig. 2b** and **Supplementary Table 2**). These results indicate that the experience of pleasure while listening to music is associated with dopamine release in striatal reward systems.

fMRI data: temporal specificity of reward responses

To gain information about the dynamics of dopamine release over time, we acquired fMRI scans during presentation of pleasurable and neutral music excerpts. Listeners indicated by button press when they experienced chills (mean = 3.1 chills per excerpt, s.d. = 0.9); these responses

were then used *post hoc* to identify anticipation and peak experience time periods (**Fig. 3a**). Anticipation epochs were defined as 15 s before the peak experiences. BOLD responses for each of these epochs were compared with periods in which participants reported feeling neutral during the same musical excerpts. The result of this contrast for each of the events was then spatially conjoined with a mask of regions that had released dopamine according to the [^{11}C]raclopride PET scan. We found that hemodynamic activity in the regions showing dopamine release was not constant throughout the excerpt, but was restricted to moments before and during chills and, critically, was anatomically distinct. During peak pleasure experience epochs, as compared with neutral epochs, there was increased BOLD response in the right NAcc ($x, y, z = 8, 10, -8$; $t = 2.8$; **Fig. 3b**). In contrast, increased BOLD response was also found during the anticipation epochs, but was largely confined to the right caudate ($x, y, z = 14, -6, 20$; $t = 3.2$; **Fig. 3b**).

The temporal dynamics of the reward response and its relationship to the caudate and NAcc clusters can be more specifically analyzed by examining the percent BOLD signal change occurring over time in relation to peak pleasure. To avoid the ‘circularity’ problem²², we

Figure 4 Brain and behavior relationships involving temporal components of pleasure during music listening. Left, coronal slices showing binding potential differences in dorsal (top) and ventral (bottom) striatum that also show hemodynamic activity during anticipation versus experience of chills, respectively. Right, behavioral ratings of the number and intensity of chills and pleasure reported during the PET scans plotted against [^{11}C]raclopride binding potential changes in the two clusters. The number of chills reported was positively correlated with percent binding potential change in the caudate ($*P < 0.05$), which was linked to BOLD response immediately preceding chills (that is, anticipatory periods), consistent with the idea that a greater number of chills would result in greater anticipation and result in more activity in the areas associated with anticipation. The mean intensity of chills and reported pleasure were positively correlated with the NAcc ($**P < 0.01$), which was linked to BOLD response during chills, confirming that this region is involved in the experience of the highly pleasurable component of music listening.

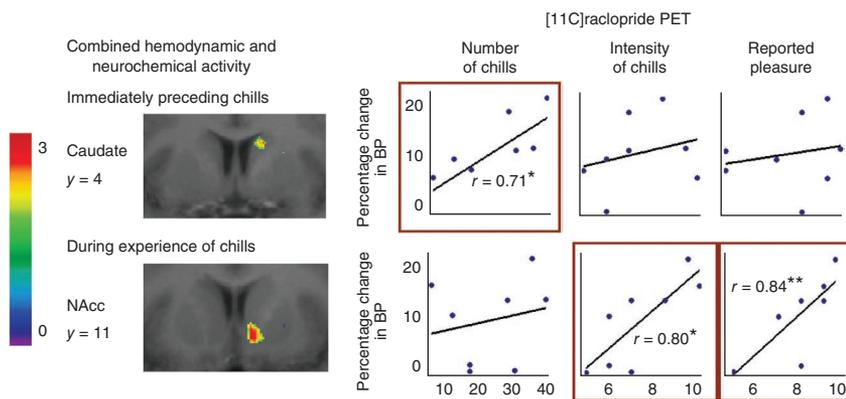
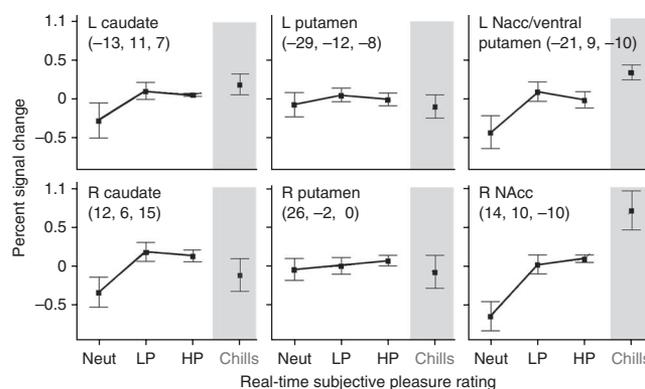


Figure 5 Brain and behavior relationships involving parametric increases in pleasure during music listening. Relationship between real-time ratings of pleasure during music listening and percent BOLD signal change relative to the mean in regions showing dopamine release as identified via PET. The chills epochs (shaded) were excluded from the analysis (values shown here only for reference) to examine activity related to increases in pleasure irrespective of chills. A regression analysis revealed that the NAcc, and to a lesser extent the left and right caudate, significantly predicted increases in pleasure ratings during each of the conditions ($P < 0.05$ and $P < 0.001$, respectively; **Supplementary Table 4**). This analysis indicates that activity in these regions increased with pleasure even when no chills were experienced. LP, low pleasure; HP, high pleasure.



derived our voxels of interest (VOIs) from the PET data, which are independent of the fMRI data. This procedure also allowed us to better integrate the hemodynamic and neurochemical results. We found that activity in both the caudate and NAcc was increased during anticipation as compared with the mean signal during the neutral epochs for the same pieces of music, with larger increases occurring in the caudate (Fig. 3c). During the peak emotional response, however, activity in the caudate decreased, whereas activity in the NAcc continued to increase. These findings support our fMRI contrast results and provide temporal information as to how hemodynamic activity in the regions showing dopamine release may contribute to reward processing in real time.

Brain-behavior relationships

Once we had identified, via fMRI, the caudate and NAcc as contributing to the anticipation and experience, respectively, of peak pleasure moments during music listening, we used our PET scan data to further explore the brain and behavior relationships in these clusters. Mean [^{11}C]raclopride binding potential values from the NAcc and caudate clusters was plotted against behavioral data obtained during PET scanning, which required participants to indicate the total number of chills, mean intensity of chills and mean subjective pleasure experienced during each piece of music. We found that the number of chills was significantly correlated ($P < 0.05$) with binding potential differences in the right caudate, but not the NAcc, whereas the intensity of chills and overall degree of pleasure experienced were most significantly correlated ($P < 0.01$) with binding potential change in the right NAcc, but not the caudate (Fig. 4 and **Supplementary Table 3**). This finding further supports a functional dissociation in the contribution of these anatomical regions to pleasure associated with music listening.

An additional question is whether increases in pleasure alone, in the absence of chills, result in increased hemodynamic responses in the same areas as during the experience of chills, although perhaps not to the same extent. We examined this question by determining whether there was a linear relationship between increases in pleasure and hemodynamic activity in the right NAcc, irrespective of chills, and how this compared with other striatal regions showing dopamine release. This analysis was done by excluding all of the epochs during which individuals experienced chills and examining BOLD signal changes that related to increasing pleasure in the right NAcc. Using the voxel that showed the maximum dopamine release in the NAcc during the [^{11}C]raclopride scan, we calculated the percent BOLD signal change as subjective pleasure ratings increased from neutral to low pleasure to high pleasure (excluding chills) for each individual. Note that this analysis, unlike the one presented above, does not take into account the temporal component, as all epochs rated as having the same pleasure were averaged, regardless of when they occurred with respect to chills. A regression analysis

revealed a significant linear trend in which the percent signal change in the right NAcc accounted for 67% of the variability in subjective pleasure ratings ($t(19) = 6.18$, $P < 0.001$). This finding suggests that increases in subjective pleasure correspond to increases in neural activity in the NAcc, in the same regions as those involved in the chills responses and those that showed dopamine release in the PET study, even though this analysis excluded all chills epochs.

Next, to ensure that increases in pleasure, irrespective of chills, are not better predicted by activity in regions of the striatum other than the right NAcc, we performed a similar analysis in all anatomical clusters that had shown dopamine release in the PET study. We first selected peak voxels from each cluster showing dopamine release from the PET data and then extracted the percent BOLD signal change as listeners reported increases in pleasure from the fMRI data; as before, all chills epochs were excluded. A stepwise multiple regression analysis was performed to examine which cluster's hemodynamic responses were best able to predict pleasure states. We found that hemodynamic increase in the NAcc cluster was the most significant predictor ($P < 0.01$) of increasing subjective pleasure (**Supplementary Table 4**). However, at a lower statistical threshold of $P < 0.05$, bilateral caudate clusters and the left NAcc/ventral putamen cluster could also predict pleasure states, but to a lower degree (31% and 43% for left and right caudate, respectively, and 37% for the NAcc/ventral putamen). Recruitment of the caudate is not surprising considering that anticipatory periods result in a culmination of pleasurable emotional experiences and the caudate was recruited during these pleasant anticipatory moments. Indeed, the mean subjective pleasure rating provided by listeners during the anticipatory epochs was 2.51 (s.d. = 0.55), which was significantly higher than that of the entire excerpt (mean = 2.11, s.d. = 0.019; $t(246) = 8.5$, $P < 0.001$).

Finally, when the percent BOLD signal change during the chills epochs was included in the multiple regression analysis (Fig. 5), it was apparent that the experience of chills represents the highest point of hemodynamic activity in the NAcc. These findings converge to suggest that the dorsal and ventral subdivisions of the striatum are most involved during anticipation and experience of the peak emotional responses during music listening, respectively.

DISCUSSION

Our results provide, to the best of our knowledge, the first direct evidence that the intense pleasure experienced when listening to music is associated with dopamine activity in the mesolimbic reward system, including both dorsal and ventral striatum. This phylogenetically ancient circuitry has evolved to reinforce basic biological behaviors with high adaptive value. However, the rewarding qualities of music listening are not obviously directly adaptive. That is, musical stimuli,

similar to other aesthetic stimuli, are perceived as being rewarding by the listener, rather than exerting a direct biological or chemical influence. Furthermore, the perception that results in a rewarding response is relatively specific to the listener, as there is large variability in musical preferences amongst individuals. Thus, through complex cognitive mechanisms, humans are able to obtain pleasure from music², a highly abstract reward consisting of just a sequence of tones unfolding over time, which is comparable to the pleasure experienced from more basic biological stimuli.

One explanation for this phenomenon is that it is related to enhancement of emotions^{3,15,20}. The emotions induced by music are evoked, among other things, by temporal phenomena, such as expectations, delay, tension, resolution, prediction, surprise and anticipation^{11,19}. Indeed, we found a temporal dissociation between distinct regions of the striatum while listening to pleasurable music. The combined psychophysiological, neurochemical and hemodynamic procedure that we used revealed that peaks of ANS activity that reflect the experience of the most intense emotional moments are associated with dopamine release in the NAcc. This region has been implicated in the euphoric component of psychostimulants such as cocaine²³ and is highly interconnected with limbic regions that mediate emotional responses, such as the amygdala, hippocampus, cingulate and ventromedial prefrontal cortex²⁴. In contrast, immediately before the climax of emotional responses there was evidence for relatively greater dopamine activity in the caudate. This subregion of the striatum is interconnected with sensory, motor and associative regions of the brain^{24,25} and has been typically implicated in learning of stimulus-response associations^{24,26} and in mediating the reinforcing qualities of rewarding stimuli such as food²⁷. Our findings indicate that a sense of emotional expectation, prediction and anticipation in response to abstract pleasure can also result in dopamine release, but primarily in the dorsal striatum. Previous studies have found that amphetamine-induced dopamine release in the NAcc spreads to more dorsal regions after repeated exposure to the drug²⁸, which suggests that this area may be involved in improved predictability and anticipation of a reward. Similarly, previous studies involving rewards such as food and smoking that contain a number of contextual predicting cues (for example, odor and taste) also found dorsal striatum dopamine release^{27,29}. Conversely, in studies in which there were no contextual cues or experience with the drugs involved, dopamine release was largely observed in the ventral striatum^{30,31}. Finally, evidence from animal research also suggests that, as rewards become better predicted, the responses that initiated in the ventral regions move more dorsally in the striatum³². These results are consistent with a model in which repeated exposure to rewards associated with a specific context gradually shift the response from ventral to dorsal and further suggest that contextual cues that allow prediction of a reward, in our case the sequences of tones leading up to the peak pleasure moments, may also act as reward predictors mediated via the dorsal striatum.

Another noteworthy finding is the correspondence between behavioral and imaging results, which strengthens the evidence for the distinct roles of dorsal and ventral striatum. We found a positive correlation between subject-reported intensity of chills and dopamine release in the NAcc during [¹¹C]raclopride PET scanning (Fig. 4), which confirms the fMRI results that peak pleasure responses are associated with this region. Furthermore, the number of chills reported by listeners during the PET scan was correlated with dopamine release in the caudate (Fig. 4), which is consistent with the fMRI results showing increased activity in this region during anticipation of peak emotional responses; as greater number of chills suggests increased incidence of anticipation, greater dopamine release would be expected in this area.

It is important to note that chills are not necessarily pleasurable *per se*, as they can be unpleasant in other contexts (for example, as a result of intense fear). Instead, chills are physiological markers of intense ANS arousal^{5,15,33,34}, which in turn is believed to underlie peak pleasure during music listening^{5,15}; we used chills here only to allow objective quantification of a highly subjective response that would be otherwise difficult to measure and because they afford precision as to the time at which the peak pleasure occurred. As such, chills are byproducts, and not a cause of the emotional responses. Thus, it is important to clarify that, although chills index peak emotional responses in this group of people, the specific experience of chills is not necessary to result in neural activity in the striatum, a finding that is consistent with less-specific analyses performed in previous studies^{6–8}. This conclusion is confirmed by our findings that, even when the chills epochs were excluded from the analysis, there was still a significant linear relationship between increases in self-reported pleasure and increases in hemodynamic activity in the regions that showed dopamine release (Fig. 5). Furthermore, when chills were reported, maximal signal was seen in the NAcc voxels that showed a linear increase as participants progressed from neutral to low pleasure to high pleasure, further confirming that chills represented the peak of pleasure in this group. This finding is also consistent with the finding that the degree of binding potential decrease in the NAcc for each participant was positively correlated with the degree of pleasure reported from listening to the musical excerpts, irrespective of the number of chills that were experienced (Fig. 4).

It should be noted that there was some activity in the ventral striatum during the anticipation phase at lower statistical thresholds, consistent with other studies using different stimuli²⁴. However, we found that, during the anticipatory phase, there was also increased BOLD response in the caudate (more so than the NAcc), which then shifted more ventromedially as participants reported experiencing peak reward (Fig. 3). This is an important finding because the stimulus that we are using is a dynamic reward with a temporal component, allowing examination of the reward in real time as it progresses from anticipation to peak pleasure states, which is generally not possible because of limitations with movement inside the PET scanner. Some studies administered the pleasurable stimulus (for example, food) immediately before the scan and measured subsequent dopamine release²⁷, in which case anticipation and consumption cannot be distinguished. Other studies measured the anticipation phase online, with the promise of the delivery of the tangible reward after the scan, in which case the consumption phase is missed^{35,36}. Music is a unique reward that allows assessment of all reward phases online, from the point that a single note is heard to the point at which maximum pleasure is reached.

The anatomical dissociation between the anticipatory and consummatory phases during intensely pleasurable music listening suggests that distinct mechanisms are involved. This distinction may map onto the 'wanting' and 'liking' phases of a reward in an error prediction model³⁷. The anticipatory phase, set off by temporal cues signaling that a potentially pleasurable auditory sequence is coming, can trigger expectations of euphoric emotional states and create a sense of wanting and reward prediction. This reward is entirely abstract and may involve such factors as suspended expectations and a sense of resolution. Indeed, composers and performers frequently take advantage of such phenomena, and manipulate emotional arousal by violating expectations in certain ways or by delaying the predicted outcome (for example, by inserting unexpected notes or slowing tempo) before the resolution to heighten the motivation for completion. The peak emotional response evoked by hearing the desired sequence would

represent the consummatory or liking phase, representing fulfilled expectations and accurate reward prediction. We propose that each of these phases may involve dopamine release, but in different sub-circuits of the striatum, which have different connectivity and functional roles.

The notion that dopamine can be released in anticipation of an abstract reward (a series of tones) has important implications for understanding how music has become pleasurable. However, the precise source of the anticipation requires further investigation. A sense of anticipation may arise through one's familiarity with the rules that underlie musical structure, such that listeners are anticipating the next note that may violate or confirm their expectations, in turn leading to emotional arousal, or alternatively it may arise through familiarity with a specific piece and knowing that a particularly pleasant section is coming up¹¹. These components are not mutually exclusive, as the second likely evolves from the first, and the overall anticipation is likely to be a combination of both. Nonetheless, the subtle differences that exist between them will need to be disentangled through future experiments that are specifically designed to parse out this distinction. Abstract rewards are largely cognitive in nature and our results pave the way for future work to examine nontangible rewards that humans consider rewarding for complex reasons.

Dopamine is pivotal for establishing and maintaining behavior. If music-induced emotional states can lead to dopamine release, as our findings indicate, it may begin to explain why musical experiences are so valued. These results further speak to why music can be effectively used in rituals, marketing or film to manipulate hedonic states. Our findings provide neurochemical evidence that intense emotional responses to music involve ancient reward circuitry and serve as a starting point for more detailed investigations of the biological substrates that underlie abstract forms of pleasure.

METHODS

Methods and any associated references are available in the online version of the paper at <http://www.nature.com/natureneuroscience/>.

Note: Supplementary information is available on the Nature Neuroscience website.

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AUTHOR CONTRIBUTIONS

V.N.S., R.J.Z. and A.D. designed the study. V.N.S. and M.B. performed all experiments. V.N.S., M.B. and K.L. analyzed the data. V.N.S. and R.J.Z. wrote the manuscript.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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1. Egerton, A. *et al.* The dopaminergic basis of human behaviors: a review of molecular imaging studies. *Neurosci. Biobehav. Rev.* **33**, 1109–1132 (2009).
2. Dube, L. & Lebel, J. The content and structure of laypeople's concept of pleasure. *Cogn. Emot.* **17**, 263–295 (2003).
3. Sloboda, J. & Juslin, P.N. Psychological perspectives on music and emotion. in *Music and Emotion: Theory and Research* (ed. Sloboda, J.) 71–104 (Oxford University Press, Oxford, 2001).

4. Krumhansl, C.L. An exploratory study of musical emotions and psychophysiology. *Can. J. Exp. Psychol.* **51**, 336–353 (1997).
5. Blood, A.J. & Zatorre, R.J. Intensely pleasurable responses to music correlate with activity in brain regions implicated in reward and emotion. *Proc. Natl. Acad. Sci. USA* **98**, 11818–11823 (2001).
6. Menon, V. & Levitin, D.J. The rewards of music listening: response and physiological connectivity of the mesolimbic system. *Neuroimage* **28**, 175–184 (2005).
7. Koelsch, S., Fritz, T., Cramon, D., Müller, K. & Friederici, A.D. Investigating emotion with music: an fMRI study. *Hum. Brain Mapp.* **27**, 239–250 (2006).
8. Mitterschiffthaler, M.T., Fu, C.H.Y., Dalton, J., Andrew, C.M. & Williams, S. A functional MRI study of happy and sad affective states induced by classical music. *Hum. Brain Mapp.* **28**, 1150–1162 (2007).
9. Knutson, B. & Gibbs, S.E. Linking nucleus accumbens dopamine and blood oxygenation. *Psychopharmacology (Berl.)* **191**, 813–822 (2007).
10. Laruelle, M. Imaging synaptic neurotransmission with *in vivo* binding competition techniques: a critical review. *J. Cereb. Blood Flow Metab.* **20**, 423–451 (2000).
11. Huron, D. & Hellmuth Margulis, E. Musical expectancy and thrills. in *Music and Emotion* (eds. Juslin, P.N. & Sloboda, J.) (Oxford University Press, New York, 2009).
12. Grewe, O., Nagel, F., Kopiez, R. & Altenmüller, E. Emotions over time: synchronicity and development of subjective, physiological, and facial affective reactions to music. *Emotion* **7**, 774–788 (2007).
13. Panksepp, J. The emotional source of “chills” induced by music. *Music Percept.* **13**, 171–207 (1995).
14. Sloboda, J. Music structure and emotional response: some empirical findings. *Psychol. Music* **19**, 110–120 (1991).
15. Salimpoor, V.N., Benovoy, M., Longo, G., Cooperstock, J.R. & Zatorre, R.J. The rewarding aspects of music listening are related to degree of emotional arousal. *PLoS ONE* **4**, e7487 (2009).
16. O'Doherty, J.P., Deichmann, R., Critchley, H.D. & Dolan, R. Neural responses during anticipation of a primary taste reward. *Neuron* **33**, 815–826 (2002).
17. Schultz, W., Dayan, P. & Montague, P.R. A neural substrate of prediction and reward. *Science* **275**, 1593–1599 (1997).
18. Wise, R.A. Dopamine, learning and motivation. *Nat. Rev. Neurosci.* **5**, 483–494 (2004).
19. Huron, D. *Sweet Anticipation: Music and the Psychology of Expectation* (MIT Press, Cambridge, Massachusetts, 2006).
20. Meyer, L.B. *Emotion and Meaning in Music*. (University of Chicago Press, Chicago, 1956).
21. Schott, B.H. *et al.* Mesolimbic functional magnetic resonance imaging activations during reward anticipation correlate with reward-related ventral striatal dopamine release. *J. Neurosci.* **28**, 14311–14319 (2008).
22. Kriegeskorte, N., Simmons, W.K., Bellgowan, P.S. & Baker, C.I. Circular analysis in systems neuroscience: the dangers of double dipping. *Nat. Neurosci.* **12**, 535–540 (2009).
23. Volkow, N.D. *et al.* Relationship between subjective effects of cocaine and dopamine transporter occupancy. *Nature* **386**, 827–830 (1997).
24. Haber, S. & Knutson, B. The reward circuit: linking primate anatomy and human imaging. *Neuropharmacology* **35**, 4–26 (2010).
25. Haber, S.N., Kim, K.S., Maily, P. & Calzavara, R. Reward-related cortical inputs define a large striatal region in primates that interface with associative cortical connections, providing a substrate for incentive-based learning. *J. Neurosci.* **26**, 8368–8376 (2006).
26. Valentin, V.V. & O'Doherty, J.P. Overlapping prediction errors in dorsal striatum during instrumental learning with juice and money reward in the human brain. *J. Neurophysiol.* **102**, 3384–3391 (2009).
27. Small, D.M., Jones-Gotman, M. & Dagher, A. Feeding-induced dopamine release in dorsal striatum correlates with meal pleasantness ratings in healthy human volunteers. *Neuroimage* **19**, 1709–1715 (2003).
28. Boileau, I. *et al.* Modeling sensitization to stimulants in humans: an [11C]raclopride/positron emission tomography study in healthy men. *Arch. Gen. Psychiatry* **63**, 1386–1395 (2006).
29. Barrett, S.P., Boileau, I., Okker, J., Pihl, R.O. & Dagher, A. The hedonic response to cigarette smoking is proportional to dopamine release in the human striatum as measured by positron emission tomography and [11C]raclopride. *Synapse* **54**, 65–71 (2004).
30. Leyton, M. *et al.* Amphetamine-induced increases in extracellular dopamine, drug wanting, and novelty seeking: a PET/[11C]raclopride study in healthy men. *Neuropsychopharmacology* **27**, 1027–1035 (2002).
31. Boileau, I. *et al.* Alcohol promotes dopamine release in the human nucleus accumbens. *Synapse* **49**, 226–231 (2003).
32. Everitt, B.J. & Robbins, T. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nat. Neurosci.* **8**, 1481–1489 (2005).
33. Rickard, N.S. Intense emotional responses to music: a test of the physiological arousal hypothesis. *Psychol. Music* **32**, 371–388 (2004).
34. Grewe, O., Kopiez, R. & Altenmüller, E. Chills as an indicator of individual emotional peaks. *Ann. NY Acad. Sci.* **1169**, 351–354 (2009).
35. Zald, D.H. *et al.* Dopamine transmission in the human striatum during monetary reward tasks. *J. Neurosci.* **24**, 4105–4112 (2004).
36. Koeppe, M.J. *et al.* Evidence for striatal dopamine release during a video game. *Nature* **393**, 266–268 (1998).
37. Zald, D.H. & Zatorre, R.J. On music and reward. in *The Neurobiology of Sensation and Reward* (ed. Gottfried, J.A.) (CRC Press, 2011).

ONLINE METHODS

Participant screening and stimulus selection. 217 individuals responded to advertisements requesting people who experience chills to music; after five rounds of screening, the final group included eight participants. First, individuals provided ten pieces of instrumental music to which they experience intense pleasure and “chills” without restrictions to the genre of music, which included classical, folk, jazz, electronica, rock, punk, techno and tango (see http://www.zlab.mcgill.ca/supplements/supplements_intro.html for samples). Next, an email questionnaire was completed to determine whether their chills were experienced at times of extreme pleasure, consistently at the same point in the music without diminishing on multiple listening, in different environments, and the selected music was not specifically or generally associated with an episodic memory. 45 individuals continued to the third screening session, where a history of medical, psychiatric illness, or substance abuse was ruled out. 40 participants continued to the fourth screening session, where control stimuli were selected for each individual using a paradigm where one individual’s pleasurable music is used as another person’s neutral music^{5,15}. This way, group-averaged data analysis involves comparison of similar sets of stimuli. Although we were not able to match perfectly between the control and pleasurable pieces used for all participants, efforts were made to ensure that pieces were as evenly distributed as possible. Each individual rated other participants’ music on a scale of 1–10 (neutral to extremely pleasurable). From the pieces rated neutral, the ones that were most familiar to that subject were selected to minimize differences in familiarity between pleasurable music and neutral music conditions. Individuals whose music was found to be “neutral” by at least one other participant were asked to continue. Participants were asked not to listen to those pieces anymore during the course of the study to ensure maximal responses during testing. 28 individuals participated in the final screening session to verify the chills response at prespecified times through subjective and physiological responses. Participants listened to their chills-inducing music while providing subjective ratings of pleasure through button presses and indicating when they experienced a chill (see ref. 15 for additional details). The ten participants (five female, five male) who most reliably experienced chills during their peak pleasure responses to music accompanied by clear increases in ANS activity were selected for the study. The final group of participants was between the ages of 19 and 24 ($M = 20.8, \pm 1.9$ years) and had a wide range of musical experiences from no training to 15 years of experience.

Procedures. Ethical approval for the study was granted by the Montreal Neurological Institute (MNI) Research Ethics Board. All individuals gave written informed consent before participating in the study. Testing took place over three sessions. The first two sessions involved PET scanning (**Supplementary Fig. 1**) and psychophysiological recording (**Supplementary Fig. 2**) and the third session involved fMRI scanning (**Supplementary Fig. 3**).

Statistical analysis. Signal filtering was performed to remove noise and artifacts (see ref. 15 for additional details). Data were downsampled to 1-s epochs and compared across neutral music and pleasurable music conditions. To account for unequal variances across conditions, we used Welch’s *t* test. A second analysis was performed to examine the relationship between the intensity of chills experienced and psychophysiological responses. Outliers beyond four s.d. from the mean were removed for each excerpt and for each participant individually (2–5% of the data points). Subjective ratings for one individual were not recorded and BVP amplitude data for one participant demonstrated excessive artifacts, thus these data were not included in the analysis. *Z* score values of each biosignal were calculated for each excerpt and plotted against subjective ratings of chills intensity that subjects reported after hearing each excerpt (**Fig. 1**). Correlation coefficients were calculated for the intensity of chills and changes in each of the psychophysiological measures (**Supplementary Table 1**).

For [¹¹C]raclopride PET, we discarded two datasets because of participant discomfort during the first session. Data from the remaining eight participants were analyzed. PET emission frames were reconstructed and corrected for gamma ray attenuation and scatter. All PET images were corrected for head motion using a co-registration-based method, which performs interframe realignment and compensates for emission-transmission mismatches³⁸. The motion-corrected PET data were summed over the time dimension and aligned to the subject’s anatomical magnetic resonance image. Anatomical MRI were transformed into standardized stereotaxic space by means of automated feature

matching algorithm to the MNI template³⁹. All transformed images were visually inspected to ensure that there were no alignment errors.

Parametric images were generated in the native PET space by computing [¹¹C]raclopride binding potential (binding potential = B_{avail} / K_D , where B_{avail} is the density of available receptors and K_D is the dissociation constant) at each voxel of interest^{40,41}. Voxelwise [¹¹C]raclopride binding potential was calculated using a simplified reference region method^{40,41}, with the cerebellum chosen as reference region because it does not contain specific D₂ receptor-like binding sites and can be used for the determination of nonspecific binding and free radioligand in the brain⁴². The gray matter of the cerebellum assigned as reference region was initially segmented in Talairach space from a probabilistic atlas⁴³ and a neural net classifier⁴⁴. The [¹¹C]raclopride binding potential maps were then transformed into MNI space³⁹ using the previously determined transformation parameters. Statistical parametric *t* maps of binding potential change were produced by comparing the parametric binding potential maps of the two scan sessions (pleasurable music and neutral music), using a previously described method⁴⁵. This calculation uses the residuals of the least-squares fit of the compartmental model, which improves the sensitivity to small changes by providing better estimates of the s.d. at the voxel and by increasing the degrees of freedom. It is assumed that a reduction in [¹¹C]raclopride binding potential is indicative of an increase in extracellular dopamine concentration⁴⁶. Clusters of significant change were defined as all contiguous striatal voxels on the *t* map exceeding a magnitude threshold of 3.11. This threshold was considered to be significant ($P < 0.05$, corrected for multiple comparisons) for a search volume equal to the striatum and an effective spatial resolution of 8-mm full-width at half maximum (FWHM)⁴⁷. Mean binding potential values were extracted from each significant cluster for each individual and percent change in binding potential was calculated as $[(BP_{\text{neutral}} - BP_{\text{pleasurable}}) \times 100 / BP_{\text{neutral}}]$, and compared with subjectively reported post-listening ratings of the number of chills, intensity of chills and degree of pleasure experienced.

fMRI. One scan was terminated because of claustrophobia. fMRI data were corrected for motion using in-house software. To increase the signal-to-noise ratio, we spatially smoothed the images (or low-pass filtered) with an 8-mm FWHM isotropic Gaussian kernel. Image analyses were performed with fMRISTAT, which consists of a series of MATLAB scripts that utilize the general linear model for analyses⁴⁸. The general linear model ($Y = X\beta + \epsilon$) expresses the response variable (BOLD signal) *Y* in terms of a linear combination of explanatory variables (events) *X*, the parameter estimates (effects of interest) β and the error term ϵ . Temporal drift was modeled as cubic splines and removed by inclusion into the general linear model as a variable of non-interest. The linear model was solved for the parameter estimates β with least squares, yielding estimates of effects, standard errors and *t* statistics for each contrast and for each run.

Before group statistical maps for each contrast of interest were generated, in-house software was used to linearly transform anatomical and functional images from each subject into standard MNI stereotaxic coordinate space using the MNI 305 template³⁹. A mixed-effects linear model was subsequently used to combine data across subjects; the s.d. images were smoothed with a Gaussian filter so that the ratio of the random-effects variance divided by the fixed-effects variance results in approximately 100 degrees of freedom. Because the main purpose of the fMRI analyses was to measure BOLD activity in predefined striatal regions, we adopted an uncorrected statistical threshold of $P < 0.01$.

For the main analysis, three events were defined: the peak emotional response (PER) condition represented all epochs during which the participant was pressing the chills, the anticipation condition represented 15-s epochs immediately preceding the onset of the PER condition defined *post hoc*, and the neutral condition represented all epochs during which participants were pressing down the neutral button. Note that these neutral epochs are different from the neutral music condition, which were not used in this case, as the neutral music condition contrasted with the pleasurable music condition shows less activity in the striatum. As such, any epoch selected from the pleasurable music condition, even those not related to peak pleasure, could have shown increased striatal activity and overestimated the results of the study. The anticipation period was defined as the 15 s before the PER based on previous findings that this is the time frame during which psychophysiological responses begin to increase significantly relative to mean responses throughout the excerpt¹⁵. The times at which participants pressed the low pleasure and high pleasure buttons were also included in the model to ensure

that they did not contribute to baseline. A 0.1-s epoch was incorporated into the model each time a button was pressed to account for neural activity involved in button pressing. The BOLD data from times when participants were responding to questions were excluded from the analysis. The planned comparisons for the main analysis were then entered into the analysis: anticipation of PER = anticipation condition minus neutral condition and experience of PER = PER condition minus neutral condition.

Time series analysis. To further investigate the temporal dynamics of the reward response, we calculated the time series of hemodynamic activity in the caudate and NAcc clusters. To avoid the circularity problem²², we derived our VOIs from the PET data, which are independent of the fMRI data. We first identified the voxel showing the maximum dopamine release during the [¹¹C]raclopride PET scan, in the caudate and NAcc clusters. We then extracted the mean signal for each VOI during the entire fMRI run obtained from each volume and calculated the percent BOLD signal change relative to the mean of the run during the epochs in which PERs were reported. Participants often experienced multiple chills one after another. For the purposes of this analysis, the percent signal change during the first chill of the series was used, which ranged in duration from 1–4 s. The BOLD response for each of those seconds is plotted in **Figure 3c**. Mean signal change for each second preceding this response for each individual, up to 15 s, was also plotted to demonstrate hemodynamic time series during the anticipation period. As a result of cardiac gating, a different number of frames were acquired for each person during this 15-s period and acquisition time varied from 2.1 to 3 s depending on the individual's heart rate. As such, the VOI values obtained at each frame were interpolated to provide an estimate of signal during each second preceding the peak response. The mean number of frames sampled for calculating time series was 5.3 (s.d. = 1.3) during anticipation and 1.6 (s.d. = 1.2) during chills. The mean signal change during neutral button presses was also calculated for each VOI separately and plotted in **Figure 3d** for reference. Finally, the percent signal change for 5 s preceding the anticipatory response were also plotted for reference.

Conjunction analysis. Because [¹¹C]raclopride binds with D2 receptors mainly in the striatum⁴⁹, our fMRI data analysis was also limited to this region, masked

by areas that showed dopamine release. A spatial conjunction analysis was performed to examine the temporal aspects of hemodynamic activity in areas that had shown changes in [¹¹C]raclopride binding potential on PET. A mask of striatal areas that had revealed substantial changes in binding potential using the stated threshold ($t \geq 3.11$) was created to spatially mask both contrasts (outlined in the fMRI data analysis section): anticipation of PER and experience of PER. This procedure allowed us to measure BOLD changes only in voxels that had shown binding potential differences in the PET study.

38. Costes, N. *et al.* Motion correction of multi-frame PET data in neuroreceptor mapping: simulation based validation. *Neuroimage* **47**, 1496–1505 (2009).
39. Collins, D.L., Peters, T.M. & Evans, A.C. Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. *J. Comput. Assist. Tomogr.* **18**, 192–205 (1994).
40. Gunn, R.N., Lammertsma, A.A., Hume, S.P. & Cunningham, V.J. Parametric imaging of ligand-receptor binding in PET using a simplified reference region model. *Neuroimage* **6**, 279–287 (1997).
41. Lammertsma, A.A. & Hume, S.P. Simplified reference tissue model for PET receptor studies. *Neuroimage* **4**, 153–158 (1996).
42. Litton, J.E., Hall, H. & Pauli, S. Saturation analysis in PET-analysis of errors due to non-perfect reference regions. *J. Cereb. Blood Flow Metab.* **14**, 358–361 (1994).
43. Collins, D.L. & Evans, A.C. ANIMAL: Validation and application of nonlinear registration-based segmentation. *Intern. J. Pattern Recognit. Artif. Intell.* **11**, 1271–1294 (1997).
44. Zijdenbos, A., Forghani, R. & Evans, A.C. Automatic quantification of MS lesions in 3D MRI Brain data sets: validation of INSECT. in *Medical Image Computing and Computer-Assisted Intervention* (eds. Wells, W.M., Colchester, A. & Delp, S.) 439–448 (Springer-Verlag, Cambridge, Massachusetts, 1998).
45. Aston, J.A. *et al.* A statistical method for the analysis of positron emission tomography neuroreceptor ligand data. *Neuroimage* **12**, 245–256 (2000).
46. Endres, C.J. *et al.* Kinetic modeling of [¹¹C]raclopride: combined PET microdialysis studies. *J. Cereb. Blood Flow Metab.* **17**, 932–942 (1997).
47. Worsley, K.J. *et al.* A unified statistical approach for determining significant signals in images of cerebral activation. *Hum. Brain Mapp.* **4**, 58–73 (1996).
48. Worsley, K.J. *et al.* A general statistical analysis for fMRI data. *Neuroimage* **15**, 1–15 (2002).
49. Slifstein, M. *et al.* Striatal and extrastriatal dopamine release measured with PET and [(18)F]fallypride. *Synapse* **64**, 350–362 (2010).