

In addition, we examined the effects of wireless tonic stimulation of VTA-DA neurons on anxiety-like behavior. Tonic stimulation at 5 Hz reduced anxiety-like behavior, whereas phasic activation of VTA-DA neurons did not have an effect on anxiety-like behavior (fig. S24). These findings are consistent with the anxiolytic actions of nicotine on VTA-DA neurons, as well as the behavioral phenotypes seen in the *ClockΔ19* mice that have increased tonic firing of VTA-DA neurons (33, 34), and further establish the utility of wireless optogenetic control in multiple environmental contexts.

These experiments demonstrate that these devices can be readily implemented in optogenetic experiments. Future possible uses are in closed-loop operation, where actuators (e.g., heat, light, and electrical) operate in tandem with sensors (e.g., temperature, light, and potential) for altering light stimulation in response to physiological parameters, such as single-unit activity, pH, blood oxygen or glucose levels, or neurochemical changes associated with neurotransmitter release. Many of the device attributes that make them useful in optogenetics suggest strong potential for broader utility in biology and medicine. The demonstrated compatibility of silicon technology in these injectable, cellular-scale platforms foreshadows sophisticated capabilities in electronic processing and biological interfaces. Biocompatible deep-tissue injection of semiconductor devices and integrated systems, such as those reported here, will accelerate progress in both basic science and translational technologies.

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Supplementary Materials

www.sciencemag.org/cgi/content/full/340/6129/211/DC1
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Interactions Between the Nucleus Accumbens and Auditory Cortices Predict Music Reward Value

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We used functional magnetic resonance imaging to investigate neural processes when music gains reward value the first time it is heard. The degree of activity in the mesolimbic striatal regions, especially the nucleus accumbens, during music listening was the best predictor of the amount listeners were willing to spend on previously unheard music in an auction paradigm. Importantly, the auditory cortices, amygdala, and ventromedial prefrontal regions showed increased activity during listening conditions requiring valuation, but did not predict reward value, which was instead predicted by increasing functional connectivity of these regions with the nucleus accumbens as the reward value increased. Thus, aesthetic rewards arise from the interaction between mesolimbic reward circuitry and cortical networks involved in perceptual analysis and valuation.

Music is a potent phenomenon, existing in all cultures from prehistory onward (1). How sounds that have no intrinsic reward value can become highly pleasurable remains largely unknown. Prior studies demonstrate that listening to music engages not only the

auditory cortices, but also emotion regions and reward-related mesolimbic circuits (2, 3); studies have also shown that dopamine mediates this response in the striatum (4). These reward circuits reinforce biologically adaptive behaviors, including eating and sex (5, 6), and are shared by most vertebrates. However, appreciation of music is complex and seemingly distinct to humans and is dependent on sociocultural factors, experience, and memory, suggesting an integrative role for cortical processes in interaction with dopamine-reinforcement circuits. Dopamine is involved in incentive salience and reward prediction, leading to expectation and anticipation

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of a desirable item (7–9). The principal affective impact of music is thought to be elicited by the creation of expectancies through temporally rooted phenomena, such as delay, anticipation, and surprise (10). Previously, functional magnetic resonance imaging (fMRI) revealed hemodynamic activity associated with anticipatory periods preceding peak pleasure moments during music listening; this activity took place in the same regions that showed dopamine release using ligand-based positron emission tomography (4). Anticipation may arise from either explicit knowledge of specific music or more implicit schematic expectancies representing rules of how sound patterns are organized (10, 11) based on culture- and person-specific musical knowledge gained through years of exposure to various musical sounds. The former can explain why we enjoy familiar music, but not how previously unheard music can be ap-

preciated. A prediction-error model (12) in which predictions are fulfilled or surpassed, mediated via a dopaminergic response (9), may shape the biological response to music based on schematic expectancies independent of explicit knowledge. To examine this hypothesis, we used new music excerpts to minimize explicit predictions, selected with the help of music-recommendation software designed to reflect individual preferences (see www.zlab.mcgill.ca/science2013/ for a list of music stimuli used in this experiment) (13). To assess reward value objectively, individuals could purchase the music with their own money, as an indication that they wanted to hear it again. To further increase ecological validity, we used an interface and prices similar to those in iTunes. While undergoing fMRI scanning, 19 participants (10 female, 9 male) (table S1) listened to 60 musical excerpts, providing bids of how much they were willing to spend

for each item in an auction paradigm (Fig. 1 and fig. S1) (14).

Whole-brain analysis of hemodynamic activity during the 30-s listening period of excerpts with bids greater than \$0 showed increased activity in the dorsal and ventral striatum, inferior frontal gyrus (IFG), insula, temporal pole, and cerebellum (Fig. 2A and table S2). To examine which of these regions are associated with reward value, we selected the 11 individuals with sufficient bids in all categories (\$0, \$0.99, \$1.29, and \$2) and at least three bids in the most expensive category. Multivariate regression revealed that reward value (amount bid) was most directly related to the degree of activity in the right nucleus accumbens (NAcc) in the ventral striatum, a key region associated with positive prediction error (15, 16); NAcc activity accounted for 33% of the variability in bids. The right caudate, a part of the dorsal

Fig. 1. Experimental paradigm. (A) Blood-oxygenation-level-dependent (BOLD) activity was collected while participants listened to 60 30-s clips of new music (matched to their preferences by music-recommendation software, such as Pandora and Last.fm). Participants then placed bids with their own money that were used to categorize each excerpt according to desirability (\$0, \$0.99, \$1.29, and \$2) for the purposes of analysis. (B) Contrast analysis revealed regions associated with purchasing (Fig. 2A). (C) Multivariate connectivity methods allowed us to examine neural interactions associated with increased reward value of music (Fig. 3).

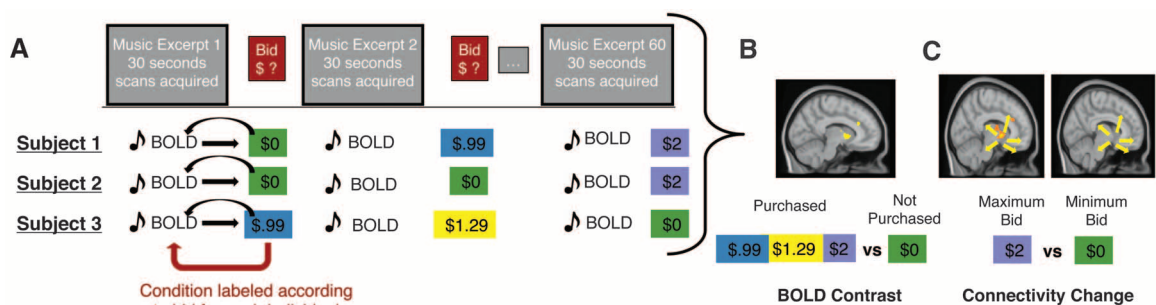


Fig. 2. Neural activity associated with reward value of music. (A) A whole-brain contrast revealed areas, including the dorsal and ventral striatum, that are active during the processing of desirable (bids > \$0) as opposed to undesirable (\$0 bids) music (table S2A). Z, plane of horizontal section (millimeters); t, value of *t* statistic; X, plane of vertical section (millimeters). (B) Among individuals who made sufficient bids in all categories (13), multiple linear regression allowed us to determine which purchasing-related regions (table S2B) corresponded to increasing reward value. Among the clusters from Fig. 1A, signal change in the right NAcc accounted for 33% of the variability in the amount spent, and the caudate accounted for an additional 10%; other regions did not contribute directly to reward value. Error bars indicate 1 SEM. (C) Average BOLD signal time course for the right NAcc and right caudate during the 30-s excerpts.

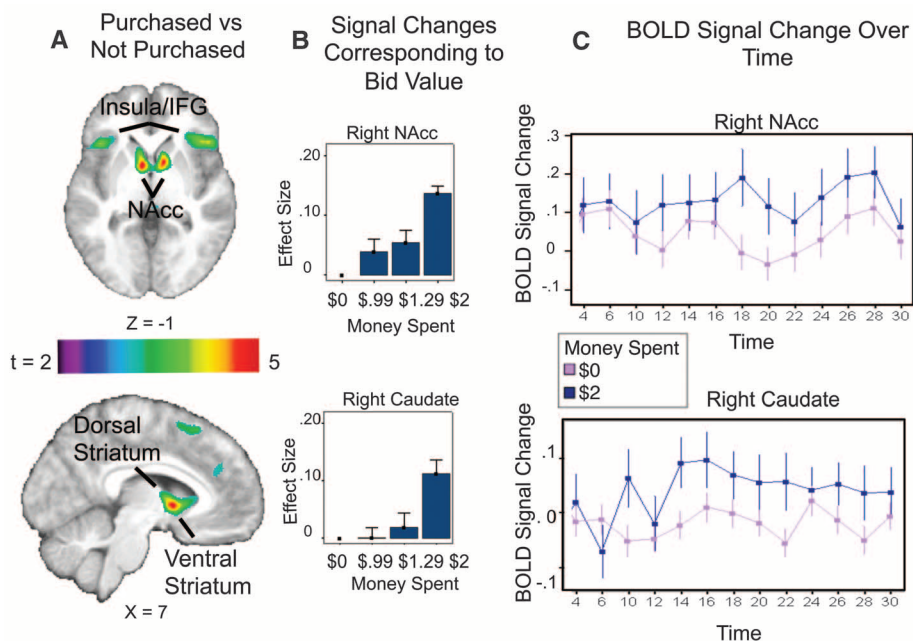
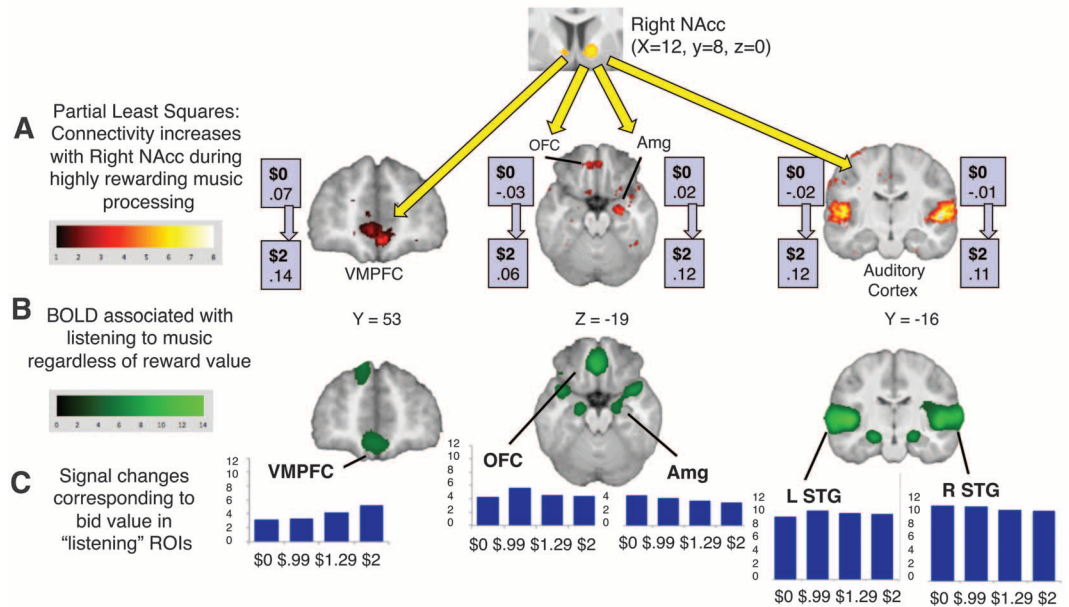


Fig. 3. Changes in NAcc functional connectivity associated with increasing desirability of music. (A) Partial least-squares analysis revealed robust increases in connectivity between the NAcc and other subcortical and cortical regions when individuals hear music they consider highly desirable, compared with music they do not want to hear again (table S3). Here, the boxes show changes in correlation as a function of amount bid between the NAcc and each region. A subset of these regions (A) overlap with areas that are recruited during music listening compared with rest (B). These areas show equally high activity during all music valuation conditions compared with rest (C), but their interactions with the NAcc increase as items become more desirable. Amg, amygdala; ROI, region of interest.



striatum, accounted for a smaller proportion of variability (10%) in bid value, whereas the other clusters (table S1) did not show a significant contribution.

We used partial least-squares analysis (17) to examine how the mesolimbic striatal areas interact with other brain regions as musical sequences gain reward value. The NAcc showed highly robust increases in functional connectivity with large portions of the superior temporal gyrus (STG), encompassing the primary and surrounding auditory cortices bilaterally when individuals listened to items they found most desirable (Fig. 3A). These same auditory regions showed increased activity during music listening as opposed to silence (Fig. 3B) and are involved in perceptual processing of music (18). Increased hemodynamic activity in these regions did not predict reward value (Fig. 3C). However, their degree of functional connectivity with the NAcc established the level of desirability of the music for the individual (Fig. 3A).

Other areas that showed an increase in functional connectivity with the NAcc as music value increased include the ventromedial prefrontal cortex (VMPFC), orbitofrontal cortex (OFC), amygdala, hippocampus, right IFG, anterior cingulate cortex, and clusters in the somatosensory and motor areas (table S3). Although activity in most of these areas was also increased in the maximum reward condition, the VMPFC, OFC, and amygdala demonstrated similar activity in all conditions, regardless of amount bid (Fig. 3C). These regions play a well-established role in emotional processing and value-guided decision-making (19, 20) and are consistently recruited for processing all musical stimuli, which suggests a role for assigning and main-

taining value of musical sound sequences as they are temporally revealed. Importantly, these brain regions show increased connectivity with the NAcc only when the sounds gain reward value for the individual (Fig. 3A). These findings suggest a mechanism for valuation of stimuli with abstract importance.

The right caudate also showed increased connectivity bilaterally with the posterior STG proportionally to bid value, suggesting a role for retrieval of previously stored sound information; other areas showing this trend included the hippocampus and the prefrontal cortex (table S4). Connectivity between the caudate and premotor areas implicated in beat processing (21) also increased during time spent listening to highly desirable sounds.

Our results show that a network of regions—similar to that from studies with other stimuli in tasks involving reward, salience, and purchasing (19, 22)—was recruited during real-time processing of desirable new music, but only the dorsal and ventral striatum demonstrated activity proportional to the reward value of the stimulus. These areas were similar to those that showed dopamine release to familiar, highly pleasant music (4). Thus, the current results show that explicit familiarity is not necessary for activity in dopamine target regions, which may also depend on implicitly formed expectations based on previously acquired musical knowledge. Further, as the temporal unfolding of novel sound sequences gains reward value, highly robust interactions occur between cortical areas that store information about sound relationships and subcortical areas involved in assessing positive prediction errors (19, 23, 24). These results collectively sug-

gest that our appreciation of new music is likely related to (i) highly individualized accumulation of auditory cortical stores based on previous listening experiences, (ii) the corresponding temporal expectations that stem from implicit understanding of the rules of music structure and probabilities of the occurrence of temporal and tonal events, and (iii) the positive prediction errors that result from these expectations. This conclusion is consistent with music-theoretic models that emphasize temporal expectations as one of the main dimensions resulting in the affective impact of music (10, 25). Here, both dorsal and ventral striatal regions were involved in these interactions, whereas in our previous study (4), the two structures were temporally dissociated according to anticipation versus experience of peak pleasure. The present finding is consistent with the idea that during music listening there may be ongoing, possibly overlapping, processes of expectancy and evaluation as musical events unfold, thus giving rise to activity in both striatal regions.

The reward value of music is abstract: It does not involve a tangible substance, but rather a combined sensory and cognitive experience that can influence one's affective state. Our data show robust interactions between sensory and affective systems: The subcortical regions work in concert with the auditory sensory cortices to establish a potentially rewarding stimulus that is experienced for the first time as desirable. The auditory cortices are involved in auditory sensory memory and imagery, extraction of sound relationships, and discrimination and organization of sound patterns (18). These cortical stores may contain templates of previously

heard sounds, making them an ideal location for feedback regarding temporal predictions, which, in combination with the NAcc, can contribute to the rewarding nature of musical sounds. These expectancies need not be confined to harmonic or metrical structure, but may also include other features of musical sounds, including timbre, loudness changes, and perhaps even the integration of verbal content when present. Further support linking musical reward with temporal expectancies and positive prediction errors comes from the finding that highly desirable items are marked by enhanced NAcc connectivity with regions of the IFG that are thought to be involved in harmonic expectancy and processing musical structure (26). As these frontal areas are more generally involved in attentional processes, sequencing, and working memory and are also connected to the STG (27), they are in prime position to integrate auditory information over time and form syntactic predictions. Music processing also involves sensory-motor interactions coupling auditory with premotor and frontal regions, a link that has also been proposed as related to musically elicited emotion (21). In summary, we show that through the temporal dimension, previously neutral cues—tones and other sound sequences that have no inherent reward value—interact with higher-order cognitive brain regions to gain incentive salience, which then influences affective brain regions and impacts behavioral decisions about the value of an abstract stimulus.

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Supplementary Materials

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Figs. S1 and S2
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Interactions Between the Nucleus Accumbens and Auditory Cortices Predict Music Reward Value

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Music Was My First Love

Why do human beings enjoy music? Salimpoor *et al.* (p. 216) combined behavioral economics with brain scanning to explore how a piece of music is considered rewarding to an individual when it is heard for the first time. They discovered that neural activity in the mesolimbic striatum during listening to a novel piece of music was the best predictor of the money listeners were willing to spend on buying the piece. These observations implicate sensory cortical areas in reward processing, which the authors attribute to the aesthetic nature of the judgment.

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