in re-modelling of other parts of the nervous system, including the memory centres of the brain in the hippocampus [10]. Here, it interacts with stress hormones secreted from the adrenal gland (cortisol in man; corticosterone in mice), mediated by the nuclear hormone glucocorticoid receptor, GR [11]. GR is known to be an important regulator of BDNF, and is thought to be the key link between early life stress effects on brain function and dendritic development, many of which can persist throughout life. We are only just starting to appreciate how nuclear hormone signaling systems couple to the circadian clockwork, and recent studies now point to a direct interaction between proteins encoded by so-called core clock genes (PERIOD, CRYPTOCHROME, REVERB) and hormone signaling pathways [12]. For instance, there is now evidence that rhythmic action of glucocorticoids may depend on oscillations of CRYPTOCHROME, which forms a physical partnership with the GR to repress its action at specific phases of the cycle [13]. So, although the authors did not explore this, one important question is whether auditory responses, and long-term effects on nerve damage, might be mediated by stress hormones, which themselves are tightly clock-controlled. Adrenal glucocorticoids will likely also be strongly activated by strong noise stimulation, but if they are key players, then the rhythmic interaction of the GR with the core clockwork of the cochlea may be involved.

Finally, there is an obvious and important practical implication for human health. Noise levels at work are controlled by a complex legal framework, which defines tolerable levels, and requires the wearing of protective hearing devices. To what extent has such legislation accounted for possible circadian effects in man, and would it not now be important to assess whether shift-workers are especially vulnerable? In addition, many people voluntarily expose themselves to excessive noise in discos and night-clubs, and anecdotal evidence suggests that this appears to be an exclusively nocturnal activity in our species. It is now important to test whether we show similar phasic effects to mice — with increased vulnerability at night. One intriguing prediction is that we might be better able to cope with noise in the night-time, since in man the daily rhythm of adrenal stress hormones rises in the day, and falls at night — the opposite to that seen in nocturnal mice.

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# Music Biology: All This Useful Beauty

**Some healthy people fail to derive pleasure from music despite otherwise preserved perceptual and reward responses. Such 'musical anhedonia' implies the existence of music-specific brain reward mechanisms, which could provide a substrate for music to acquire biological value.**

**Camilla N. Clark, Laura E. Downey, and Jason D. Warren**

Few problems in biology are as tantalising as the problem of music. Music is universal in human societies, apparently ancient and apt to generate powerful emotional responses [1]. These are all properties that a biologically salient stimulus ought to have; however, these abstract sounds serve no obvious biological purpose and, unlike language, have no straightforward messaging function. This apparent paradox has long polarised neurobiologists and philosophers alike: in one account, music had a specific role in human evolution, probably linked to emotional social signalling [2]; in the other, it is a mere neural confection, a spandrel of language [3].

One important line of evidence in support of a biological role for music is the existence of specific neural mechanisms that process it: if evolution fashioned music-specific brain systems, it is reasonable to conclude that music (or proto-music) filled some evolutionary role for our species and to ask what that role might have been. Evidence for such music-specific brain systems has mainly been adduced in patients with focal brain damage who show dissociated patterns of performance when processing music versus other kinds of complex sounds [4]. Such cases, while informative,

pose substantial challenges of interpretation.

A new study reported in this issue of *Current Biology* by Mas-Herrero *et al.* [5] sheds fresh light on this issue, by demonstrating that some healthy people derive little pleasure from music and lack autonomic responses to it, even though they perceive music normally and show preserved responses to other rewarding stimuli. Such selective 'musical anhedonia' might, by demonstrating music-specific brain reward systems, suggest how and why music acquired reward potential for the wider human population.

## Music Engages Ancient Brain Reward Systems

The new findings of Mas-Herrero *et al.* [5] build on a growing body of work delineating the neurobiological basis of musical reward. A sensory stimulus is, in general, 'rewarding' if it engenders a pleasure response that encourages behavioural repetition [1]. Music fits this bill very well: intensely pleasurable responses to music (shivers down the spine or 'chills') are specifically and reliably triggered by particular musical features — such as the resolution of tonal ambiguity [6] — and listeners typically seek to repeat the experience. Musical shiver has been shown to activate a distributed brain network including phylogenetically ancient limbic, striatal and midbrain structures that are also engaged by cocaine and sex [7]. The mesolimbic striatal dopaminergic system encodes musical reward by modulating the connectivity of nucleus accumbens with auditory cortical and other brain regions involved in the perceptual analysis and evaluation of music [8].

Mas-Herrero *et al.* [5] show that individuals with typical hedonic behavioural and autonomic (skin conductance) responses to music have comparably intense responses to other primary (biological) and secondary reinforcers of reward, notably money. This is not to argue, of course, that all these reinforcers are somehow biologically equivalent: the neurochemical response to music is complex and includes elements such as oxytocin release that are more closely aligned with social functions such as pair bonding than arousal *per se* [9]. Nevertheless, the high stake music holds in the hedonic and biological value system of many members of our species is, at the least, surprising.

## Core Components of Music Processing Show Individual Variation

Mas-Herrero *et al.* [5] contribute two crucial new pieces to the puzzle of musical reward. Firstly, they show that the reward potential of music varies widely between healthy people, and that this range includes individuals who are apparently cognitively and physiologically largely indifferent to music. Secondly, they show that such anhedonia can be selective for music.

Didn't we already suspect that some people just don't 'get' music? Now we have a rigorous neurobiological grounding for this suspicion. Musical anhedonia is shown by this new study [5] to be specific for musical reward assignment, rather than attributable to any deficiency in perceiving or recognising music or musical emotions. It is rooted in reduced autonomic reactivity rather than simply cognitive mislabelling. Moreover, it is not attributable to more general hedonic blunting, because musically anhedonic individuals show typical responses to other sources of biological and non-biological (monetary) reward.

There may be an informative analogy here with congenital amusia ('tone deafness'), which affects specific components of music perception while apparently leaving other perceptual and cognitive domains largely unscathed [10,11]. A further interesting analogy might be drawn with clinical cases of selective musical anhedonia resulting from strategic focal brain damage [12]. Musical anhedonia and tone deafness might herald a new taxonomy of specific developmental disorders of music processing to complement the large evidence base for acquired amusias [4].

## Specific Brain Circuits May Signal the Biological Value of Music

The most parsimonious interpretation of the new findings is that there are music-specific brain reward systems to which individuals show different levels of access. Mas-Herrero *et al.* [5] propose that this specificity may be instantiated in integrated profiles of connectivity across brain networks that link perceptual, evaluative and reward processing mechanisms: this suggestion sits well with previous neuroimaging work both in the healthy brain [8,13] and in selective brain network degenerations involving the coding of music versus other categories of salient stimuli [14,15].

Natural selection is itself parsimonious and the existence of specific brain substrates for music coding in turn implies that these evolved in response to some biological imperative. But what might that have been? Clues may lie in the cognitive and neuroanatomical architecture of music processing. It has been suggested that music may appeal to the inherent fondness of our species for puzzle solving, including the resolution of perceptual ambiguity intrinsic to musical scenes [16] and pattern prediction and completion [1]. Certainly the extensive linkages between the neural machinery of emotion, reward and auditory cortical mechanisms engaged during music processing would provide an ample neuroanatomical substrate for musical pattern analysis to acquire biological resonance.

How would such an abstract activity confer a reproductive or survival advantage, of the sort required for natural selection to operate? The answer may lie in the kinds of puzzles that music helped our hominid ancestors to solve (Figure 1). Arguably the most complex, ambiguous and puzzling patterns we are routinely required to analyse are the mental states and motivations of other people, with clear implications for individual success in the social milieu. Music can model emotional mental states and failure to deduce such musical mental states correlates with catastrophic inter-personal disintegration in the paradigmatic acquired disorder of the human social brain, frontotemporal dementia [17].

Furthermore, this music cognition deficit implicates cortical areas engaged in processing both musical reward and 'theory of mind' (our ability to infer the mental states of other people) [14,15,17]. Our hominid ancestors may have coded surrogate mental states in the socially relevant form of vocal sound patterns [2]. By allowing social routines to be abstracted, rehearsed and potentially modified without the substantial cost of enacting the corresponding scenarios, such coding may have provided an

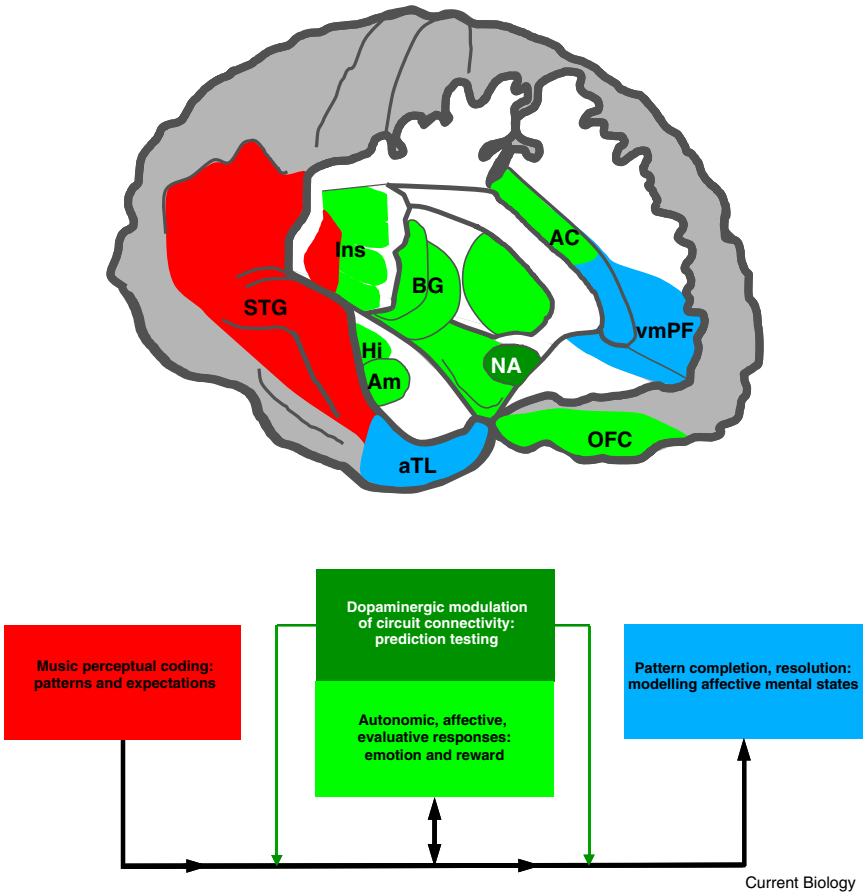


Figure 1. A neural architecture for encoding the biological value of music.

The schematic dissected brain (upper panel) shows anatomical networks implicated in music perceptual coding (red), emotion and reward processing (green) and higher-order cognitive processing (blue). Key: AC, anterior cingulate cortex; Am, amygdala; aTL, anterior temporal lobe; BG, basal ganglia; Hi, hippocampus; Ins, insula; NA, nucleus accumbens (mesolimbic striatum); OFC, orbitofrontal cortex; STG, superior temporal gyrus (and connected areas surrounding Sylvian fissure); vmPF, ventro-medial prefrontal cortex. A proposed functional architecture for information exchange between these networks — based on empirical data [1,4,7–9,12–18] — is outlined (lower panel; arrows code putative primary direction of information flow).

evolutionary mechanism by which specific brain linkages [5] assigned biological reward value to precursors of music.

## Future Directions

These new insights into musical anhedonia raise many intriguing further questions. What is its neuroanatomical basis? The strong prediction would lie with mesolimbic dopaminergic circuitry, but functional neuroimaging support is sorely needed. What are the limits of the phenomenon? Might typically musically hedonic individuals show 'musical satiety' with frequent exposure to their favourite music? The extent to which music shares a dynamic hedonic signature with, say, chocolate could illuminate the neurobiology of reward reinforcers more generally. What of the other end of the spectrum, individuals with 'musicophilia' who are hyper-hedonic for music? How does this relate to abnormal selective craving for music in some patients with temporal lobe seizures and specific neurodegenerative pathologies [18]? Such cases seem to mirror the phenomenon of musical anhedonia. More fundamentally, what are the wider implications for our understanding of other anhedonias? We have all met people who seem unmoved by food, sex or indeed, money. Is this a matter of volition, cognition or reward biology?

The current status of music as a dispensable cultural artefact (like culturally sanctioned examples of prolonged voluntary fasting or celibacy) is not necessarily a reliable guide to its neurobiological history. The work of Mas-Herrero *et al.* [5] argues that the human brain is biologically fitted to find music rewarding. The beauty we find in music, however useless it may appear, has proved useful for probing the organisation of brain reward systems. Now we must ask if music sculpted our hedonic brain architectures to more fundamentally useful neurobiological ends.

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# Plant Development: From Biochemistry to Biophysics and Back

**Since plant cells cannot move relative to each other, plant organogenesis mainly depends on the strict coordination of cell growth and proliferation. Recent work suggests that this implies a subtle combination of biochemical and physical interactions between neighboring cells.**

**Jan Traas* and Massimiliano Sassi**

Plants continuously produce new organs and tissues, which is an essential adaptation to their sessile nature. This constant growth originates from two specific types of stem cells — the shoot and root apical meristems — that are active throughout plants' life cycle. Plant cells are encased in a rigid extracellular, polysaccharidic matrix, the cell wall, which links them together and prevents any form of cell migration or sliding. For this reason, the generation of new organs in plants is a complex process that requires the coordinated regulation of cell growth and proliferation, as otherwise the differences in growth rate would tear the tissue apart. Vermeer and coworkers [1], in a study recently published in *Science,* have studied this coordination during lateral root formation, demonstrating how the coordinated behavior of two adjacent cell layers, located deep within the root, underlies the initiation of lateral root primordia (LRP).

Lateral roots are initiated in the pericycle, an inner cell layer adjacent to the vascular bundle at the center of the root, after an initial specification of the founder cells by the hormone auxin. Following this priming step, these founder cells undergo a series of asymmetric cell divisions giving rise to the meristem of the LRP [2]. The pericycle is overlaid by three other cell layers (endodermis, cortex and epidermis, from the innermost to the outermost, respectively) putting a strong mechanical constraint on the proliferation of pericycle founder cells, and thus the emergence of the LRP [3]. It was previously shown that LRP outgrowth requires the production of cell wall remodeling enzymes in the cortex and epidermis to disrupt the adhesion between adjacent cells [4]. The endodermis is far more rigid than the outer layers due to the presence of the Casparian strip, a hydrophobic, lignified structure that functions as a solute barrier isolating the vasculature from the outer environment and keeps the endodermal cells tightly connected. Vermeer and coworkers [1] show how this hurdle is taken by the LRP. As soon as the proliferation of the LRP founder cells in the pericycle begins, the overlying endodermal cells start to shrink due to the fragmentation of their vacuoles, while the fusion of the inner and outer plasma membranes creates a gap in the tissue that allows the protrusion of the primordium. The Casparian strip is only partially degraded around the gap, leaving the connections between endodermal cells largely unaltered. These events are regulated by auxin through the cell-autonomous action of the SHY2 transcriptional regulator in the endodermis [1].

Importantly, if the endodermis accommodation mechanism is impaired, as when a dominant negative version of the SHY2 protein is expressed in the endodermis, root founder cells fail to proliferate, despite the pre-existing auxin-mediated priming. The authors suggest that, in this case, the mechanical stress caused by an unaccommodating endodermis prevails, halting the genetic programme imposed by auxin. The work thus reveals what seems to be part of an interplay between biophysical and biochemical regulation, central in the formation of the LRP. This goes back to even earlier stages of lateral root specification. Previous work showed that a transient bending of the primary root, either manually imposed or caused by gravitropism, induces the formation of a LRP at the convex side of the bending [5–7]. Root bending has been proposed to somehow alter auxin concentrations in the pericycle and the adjacent vasculature by locally modifying auxin transport [5,6]. This might be due to mechanically induced changes in cell polarity, cell shape or $Ca^{2+}$ fluxes [5–7].

This mechanical regulation would, however, not be the starting point. Indeed, further upstream massive orchestrated fluctuations in gene transcription at the root tip seem to confer competence of the cells to react to the physical constraints imposed by bending [8]. From primary gene oscillations to the final breakthrough of the lateral root via mechanical priming, hormonal specification and the biochemical loosening of physical constraints, there seems to be a constant 'back-and-forth' between biochemical and biophysical regulation in the process of lateral root initiation.

This interplay between biochemical and biophysical regulation is not limited to the root. In the aerial part of the plant, the shoot apical meristem constantly generates new leaves, flowers and floral organs. Similarly to LRP development, the spatio-temporal priming of the organ primordia at the shoot apex is controlled by auxin [9]. Differently from roots, however, it is