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Toward an epigenetic view of our musical mind

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We are transient beings, in a world of constantly changing culture. At home in the fields of Art and Science, seemingly capable of magnificent abstractions, humans have an intense need to externalize their insights. Music is an art and a highly transmissible cultural product, but we still have an incomplete understanding of how our musical experience shapes and is vividly retained within our brain, and how it affects our behavior. However, the developing field of social epigenetics is now helping us to describe how communication and emotion, prime hallmarks of music, can be linked to a transmissible, biochemical change.

Keywords: music, epigenetics

A PREMISE AND SOME QUESTIONS

In 1986, Susumu Ohno published a work based on the following tenet: all music has held on the repetition of small replicating units, obsessively used by great musicians forced to plagiarize themselves, thus being easily recognizable. Similar units are found in our genetic code (Ohno and Ohno, 1986). Ohno's observations reinforce the notion that biological and cultural evolution, albeit with different speed, share similar mechanisms. Exploring such mechanisms could provide an approach to Ohno's observation that some repeating units of artistic creations are "forced" to reiterate, sometimes becoming the signature of an artist for generations to come.

But what is a creative product of the mind? An unwilling representation of the outside physical world? (Custers and Aarts, 2010). Something that emerges, almost magically, from our past experience? Is it a specific kind of action? Can our behavior, even the most ineffable (such as music our focus here) have a "genetic" and neural blueprint?

ENVIRONMENT – THE BRAIN THAT FOLLOWS, AND AN EPIGENETIC NEURONAL MEMORY

In the past decade, it has been shown that neurogenesis continues in adults, and is related to the amount of cognitive and physical stimulation to which the animal is exposed. For example, rats placed in an enriched environment, where social interaction with other rats was possible, were found to have increased neurogenesis compared to rats placed in individual cages (Gould et al., 1999). Adult neurogenesis has also been observed in primates. Indeed, it appears that about 40% of granule cells in the macaque dentate gyrus are added post-natally. Cell proliferation and neurogenesis peak during the first year, but continue to significant levels in mature monkeys (Jabes et al., 2010). In humans, neurogenesis is now thought to proceed for the entire life of individuals, if proper stimulation is available (Kuzumaki et al., 2011). Music can be such a stimulus.

Music has been an important part of human history, in all cultures. Phylogenetically, it seems likely that music has played a role in language evolution, and in supporting social functions with important evolutionary roles, such as group cohesion and communication. Making music, especially in a group, is a demanding, multi-modal task that engages the brain on many different levels, from auditory feature extraction and integration to auditory Gestalt formation, syntactic processing, learning, memory, social cognition, and action (Koelsch, 2005a,b; Koelsch et al., 2005). With the demands it places on the nervous system, musical training promotes brain plasticity, resulting in functional and structural changes. Neuroanatomical differences between musicians and non-musicians have been reported in the corpus callosum, and in motor, auditor, and visuospatial regions, including the precentral gyrus and the planum temporale. Changes in functional representations have been observed in somatosensory and auditory regions in musicians (Wan and Schlaug, 2010). Recent work by Kraus using EEG suggests that musically trained individuals might be better at encoding speech sounds (Patel, 2008). These effects are more marked in musicians who had started training in early childhood, but a few studies show that intense musical training can be effective through the lifespan, protecting the aging brain from cognitive decay (Wan and Schlaug, 2010). From a neurobiological and cognitive perspective, neural plastic changes, promoted by music fruition and training, are processes known as long-term potentiation (LTP) consisting essentially of remodeling through strengthening of existing synaptic connections. Indeed, in contextual memories, synapses are of different strength and duration depending on a number of factors, including the emotional component of a largely sensory input. The Hebbian rule "fire together, wire together" applies mostly to affective or arousal situations accompanying an event, so that neurons from different areas are simultaneously activated and will later fire together, once a new equivalent input occurs. Activation and transcription of several genes involved in excitability, transmitter release and

the maintenance of transmembrane potential is responsible for neuronal activity and LTP. Transcriptional activity, however, is preceded by structural changes of chromatin in a given set of loci and such "epigenetic" modifications must be taken into account when dealing with all cells, including neurons.

Epigenetics describes the way gene expression can change stably and be transmitted to subsequent cellular generations without modifications of the underlying coding sequence. This is achieved via the action of DNA and histone-modifying enzymes. Epigenetic changes can operate rapidly and on large fractions of the genome; they can be promptly reversible but also stable and long lasting. They can take the form of a self-sustaining and progressively strengthening feed-back loops (Krupanidhi et al., 2009). Such transcriptional–translational loops are important in a variety of situations, including circadian clock oscillators (Bellet and Sassone-Corsi, 2010).

Epigenetics is an ideal way for a fixed code to cope quickly, reversibly, and on a long range with abrupt environmental changes. In the "environmental epigenetics" hypothesis, external (including social) events can remodel the epigenome, leading to sustained alterations in its structure, delimiting transcription factor-accessible regions, and eventually generating stable effects on gene transcription (Ohta et al., 2002; Branchi, 2009; Leshem and Schulkin, 2011). Acquired epigenetic characteristics may be then transmitted both to the mitotic progeny, accounting for cell memory, and, if occurring in a proper developmental window, to subsequent generations (Leshem and Schulkin, 2011; Gilbert et al., 2012). Could such mechanisms work on largely resting, post-mitotic cells such as neurons? Could external factors epigenetically shape our brain? And on what mechanistic basis?

Rapidly accumulating evidence suggests that the adult nervous system has co-opted the same epigenetic mechanisms used to ensure cellular memory as a major tool for neural information storage, that is brain memory (Levenson et al., 2004; Levenson and Sweatt, 2005). On a molecular basis, despite many new mechanisms such as non-coding RNA (Mehler and Mattick, 2007) and prion multimerization (Si et al., 2003) have been found active in the CNS and could play a role in neuronal memory (Brown and Mastrianni, 2010) major focus is currently held on histone acetylation and the CREB/CBP system, crucial to LTP, the molecular foundation of learning and memory. For instance, HAT activity of CREB binding protein (CBP) appears critical in both long-term facilitation in *Aplysia* and the formation of long-term memory in rodents (Levine et al., 2005). In the hippocampus, following activation of NMDA receptors and extracellular signal-regulated kinase (essential events in several forms of LTP) acetylation and phosphorylation of histone H3 are increased (Reul et al., 2009). Accordingly, artificial histone acetylation using histone deacetylase (HDAC) inhibitors such as TSA or SAHA enhances induction of LTP and, importantly, the activity of the BDNF gene, a gene that promotes neurogenesis and new synaptic connections between hippocampal neurons, resulting in reinforced and expanded behavioral memory. Accordingly, old mice, compared with juveniles, exhibit reduced histone acetylation and diminished activation of learning-related genes in the hippocampus. As in the Alzheimer's mice, drugs that boosted histone acetylation improved the older mice's performance on tests of rodent cognition (Lubin, 2011).

DNA methylation also appears to be important in memory consolidation via gene-specific control of transcription, and recent studies have implicated misregulation of DNA methylation in cognitive disorders such as schizophrenia, Rett syndrome, and Fragile × mental retardation (Lubin, 2011). Interestingly, as stated above, musical training can strongly protect the aging brain from a cognitive decay, somehow paralleling the epigenetic drug treatments described in experimental models. This leads to speculate that music – at least as a learning process would presumably be capable of inducing long lasting chromatin changes, from infancy to adulthood.

A FAMILY PORTRAIT: SOCIAL EPIGENETICS, AFFECTION, AND A MUSIC SAGA

As stated above, a rich social environment is beneficial to cognitive functions, and a major molecular gear through which the environment could modify the brain is epigenetics. In rodents, early environment is mainly primed by the mother, both through nutritional and behavioral investment. Observations of mother–infant interactions in rodents during the first week postpartum show stable natural variations in maternal behavior, particularly in licking/grooming (L–G) and arched-back nursing (Champagne et al., 2006, 2007). These differences are a major determinant of the stress response of offsprings later in life (Barha et al., 2007; Champagne and Meaney, 2007; Menard and Hakvoort, 2007). Thus, offsprings born to mothers who exhibit high levels of L–G are less anxious in a novel environment and show a reduced steroid response to stress compared with offspring of low-L–G mothers. Cross-fostering studies confirm that these phenotypes are indeed mediated by variations in maternal care received during the early postpartum period (Barros et al., 2006). At the molecular level, stress responses have been associated with the estrogen and glucocorticoid receptors' expression in the brain of the pups (Champagne et al., 2006). Importantly, in offsprings of high and low-L–G mothers the promoters of these receptors show differential, albeit small, epigenetic modifications (Szyf et al., 2005; Weaver, 2007). Of note, offsprings in subsequent generations seem to maintain the phenotype, indicating a putative vertical transmission of the trait in these animals (Champagne and Meaney, 2007; Guerrero-Bosagna et al., 2010). The ability to pass such epigenetic information to the progeny may appear a far-fetched concept, given the diffuse erasing of epigenetic marks during gametogenesis (Hajkova et al., 2008) but it could well result from incomplete genome reprogramming (Rakyan et al., 2003) and may underscore an important evolutionary pressure (Molaro et al., 2011).

Correlative evidence is gathering that epigenetic modifications might occur also in humans as a response to parent–offspring interactions, which in this case are obviously far more complex than in rodents. For example, early life stress coincides with abnormal expression of the serotonin transporter gene (Caspi et al., 2003). Moreover, childhood abuse associates with an increase in pituitary ACTH responses to stress (Rinne et al., 2002) and increased methylation of the BDNF promoter and NRC3 promoter in the hippocampus has been found in suicide victims (McGowan et al., 2009); it would be interesting to investigate if similar

modifications occur in a variety of other mistreatments, including child neglect with oxytocin/vasopressin deficiency (Carter, 2005). For obvious reasons inherent with studies in humans brains which suffer the severe limitation of being applicable essentially on post-mortem subjects the formal demonstration of socially driven epigenetic changes on our species is still far ahead. This is despite the sensitive methods available: for instance, combining immunoprecipitation of methylated DNA with hybridization to tiled promoter arrays (MeDIP–CHIP) or next generation sequencing (MeDIP-Seq) allows identification of relevant methylated sequences in virtually any biological material, on a genomic scale, and without relying on a gene-candidate approach (Jacinto et al., 2008). Thus, unless one could demonstrate that epigenetic changes reflecting brain activity can be detectable on peripheral tissues (as postulated for white blood cells, see also Takao et al., 1993) perhaps we should wait further development of neuroimaging, a field improving at a great pace, and allowing studies on living subjects. Although these techniques are currently detecting solely neural activity, expectation is that in a near future they will be capable of revealing also epigenetic changes, at a high resolution. One breakthrough could be for instance to identify such modifications in an indirect way, as epigenetic proteins in action, if the removal or adding marks causes local release of detectable by-products (this is currently one way to detect *in vitro* histone demethylase LSD1's activity Huang et al., 2007).

As a cultural product, music has a special status. Despite the complexity of the cognitive operations implied by music perception, it seems that newborns and young infants are predisposed to perceive music. From the first days of life, music appears to play an important role for emotional, cognitive, and social development, and infants are surprisingly skilled at processing subtle aspects of musical stimuli (Trehub, 2003). Recently, we have shown that a few hours after birth, infants process music specifically, with a pattern of activation similar to what is observed in adults, and are sensitive to subtle structural alterations in the musical stimuli (Perani et al., 2010). Some components of our music processing skills might be genetically determined (Hose et al., 1987) although this issue is somewhat controversial: on one hand, absolute pitch recognition seems to be heritable (Drayna et al., 2001); however, the gene(s) responsible for deficits in pitch discrimination (Amusia) or Williams disease, both claimed to be transmitted via mendelian heritage (Morris and Mervis, 2000) have never been identified.

Music is also special among social activities, as it couples a message with emotions; this in turn facilitates spreading simply by imitation and self-recognition. Accordingly, emotions, especially early in life, are known to enhance learning, via serotonin-mediated modifications of glutamate receptors, the molecules responsible for plastic changes in synaptic transmission underlying learning (Xu et al., 2007). Indeed, GluR are abundantly expressed and activated by emotion, and their phosphorylation via norepinephrine (NE) lowers the threshold for synaptic incorporation during LTP in hippocampal neurons (Hu et al., 2007). Moreover, maternal care can induce thyroid hormone-dependent serotonin in the pups, and this in turn can trigger the cAMP/PKA pathway (Arnsten et al., 2005) leading to strong HAT activity (Kuo and Allis, 1998; Szyf et al., 2007) and we have already mentioned above the role of other molecules and transmitters (Guan et al., 2002; Hu et al., 2007; Liu et al., 2008). Interestingly, mother's voice, but not irrelevant voices, can protect from dopamine D1 and 5-HT1 receptors' upregulation in the anterior cingulate cortex, as it can occur in stressful conditions (Ziabreva et al., 2003). Even in pre-social species, mother's voice can suppress the upregulation of the NMDA receptor NR2B occurring after separation (Ziabreva et al., 2000) and NR2B is heavily epigenetically regulated by methylation (Kim et al., 2006; Tamura et al., 2011).

MUSIC REMAINS

Music is a universal component of human societies, helping community cohesion (rituals) and mother–child interactions, shaping offspring behavior (Chang et al., 2003). However, music should not be considered an entirely abstract exercise of the mind, being more a synesthetic object. As a tool that modulates affect and promotes the growth of emotional attachment, music might share some features with the L–G-tactile care seen naturally in the animal world, and it could bear all the crucial ingredients to determine an epigenetic change in the brain. Such changes could occur in many areas in the cortex, known to contribute to music fruition (Edeline, 1999) including the medial prefrontal cortex (Janata, 2009) and even the primary auditory cortex (Irvine and Rajan, 1996).

The notions and the literature cited so far about maternal care and gene expression in experimental animals bring us directly to the provoking parallel with the maternal care scenario seen in our species (**Figure 1**). Within this exemplar framework, could an early musical input be a human counterpart of the pure sensory and tactile stimuli, like L–G? By a "Hebbian" approach, here we see brain sculpture in action, chants, and melodies from a mother forging synapses in an ecstatic infant hearing a motherese-tuned lullaby. Within a standard cognitive framework, crucial genes participating to cell proliferation or synaptic strengthening should be activated in these neurons, and this process underlies specific epigenetic modifications, such as promoter CpG demethylation (Borrelli et al., 2008). From such repertoire, an action can later be retrieved, after an appropriate environmental input. Epigenetic marks are known to be stably transmitted to daughter cells, constituting the mechanism of cellular memory in many tissues. However, being neurons mainly post-mitotic cells, how would DNA demethylation be accomplished in the brain? Possible candidates could be arasing enzymes, such as demethylases. These recently discovered factors could actively remove repressive methyl marks even in resting cells and are thought to play a pivotal role in development (Eilertsen et al., 2007). A word of caution is necessary, though, since the actual *in vivo* role and relevance of such proteins has been questioned (see Buchen, 2010, and references therein). Of course, how can an external "social" (and actually any non-biochemical) stimulus drive epigenetic changes in the first place is a major problem of the whole (social) epigenetic field and promises to remain an unsolved conundrum for a while. What is missing is the very first scene of this play, that is the bridge between music (or any other form of human learning, for the matter) and epigenetic modifications. One possible mode could be stochasticity, where epigenetic marks are first placed randomly in early development (creating metastable epialleles) and selected afterward by the environment (Rakyan et al., 2002; Waterland et al., 2006). Alternatively, it is tempting to ask if epigenetic enzymes placing a variety of marks

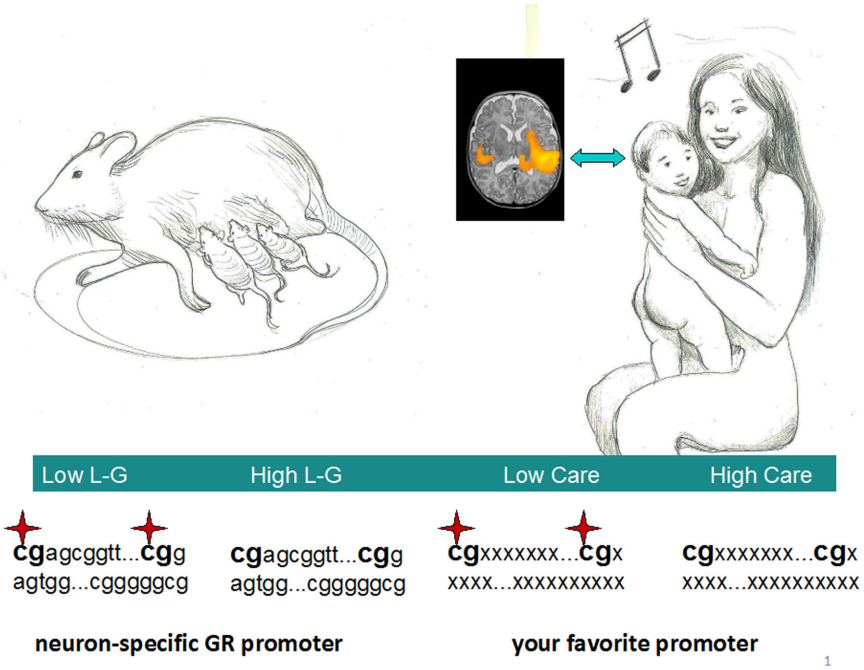

FIGURE 1 | A parallel between the maternal care scenarios in rodents and humans. Licking–grooming (L–G) in rats, usually accompanying arched-back nursing, could have a human counterpart in mothers embracing their child while chanting a lullaby. The demethylation in crucial promoters documented in rats could also occur in human neural circuits within defined brain areas. Inset shows. an fMRI image of newborns' such areas after musical stimulation. Note the right hemisphere predominance of temporal activation (adapted with permission from Perani et al., 2010). Stars represent methylated cytosines within CpG doublets.

could link social stimulations to cellular chemistry, given that some epigenetic proteins (like histone demethylases of the JMJD family and HDACs) are metal ion-dependent and an intimate connection between environmental/behavioral habits and chromatin structure has been established in cellular memory (Brasacchio et al., 2009). Obviously, his issue is still completely open to debate.

MEMES RIVISITED

In 1976 Richard Dawkins, in The Selfish Gene (Dawkins, 1976) had introduced the concept of memes, defined as: "*a new kind of replicator . . .staring us in the face; still in its infancy, still drifting clumsily about in its primeval soup, but achieving evolutionary change at a rate that leaves the old gene panting far behind.*" Dawkins describes Memes as melodies, catch phrases, ideas, insights, etc., seen as infectious particles which we use as a base to breed in our social living. In the growing branch of Memetics (Jouxtel, 2010) the rigid genetic coding lying behind the work of Ohno would be replaced by the presence of such transmissible units in our brains, behaving as selfish motors of cultural evolution. Admittedly, many questions, inherent to our discussion, remain: could neural networks endowed with epigenetic marks constitute the elusive nature of Dawkins' memes? Perhaps this nature could explain their inter-individual transmissibility, where a stored meme diffuses out, and is promptly received by others, helped by its significant affective complement. During retrieval, as in the case of music creation, these bits of information (a motif, a small melody. . .) would emerge strongly simply as a memory, due to their being embedded in long-term facilitated circuits. More intriguingly, could this epigenetic approach be a clue to understand musicians' self-sustained spiral compositions? Perhaps epigenetic-driven engrams were the source of the repetitive motifs found in Beethoven's fifth symphony, or in Chopin's Nocturne op. 55, N 1 (do-fa-mi-re-do-si-do-re-do, see Ohno and Ohno, 1986) or in Terry Ryley's or Steve Reich's compositions. Perhaps it is these self-sustaining, strengthening circuits that are behaviorally translated (and transmissed) in repetitive mantras, popular music riffs, great composers' obsessive units.

CONCLUSION

The Epigenetics Revolution is rapidly expanding its realms from the world of biochemistry to that of more immaterial objects, shaping the field of social epigenetics. Within this context, it would help explain how human relations influence our emerging creative minds in art and science. Music will shape our brain by depositing epigenetic marks and will induce some musicians to compose in a stereotypical or trance mode if you will, plagiarizing themselves and saying: "hey, this is my mind's I, I can do nothing about it!". And this music will rapidly be transmitted, floating in the environment, leaving humans with a permanent, solitary gift: an epigenetic blueprint of an emotion.

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