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The Science-Music Borderlands

Reckoning with the Past and Imagining the Future

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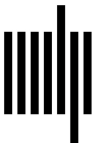
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12 Hidden Repertoires in the Brain Accessed by Music in Aging and Neurodegeneration

Sarah Faber and Randy McIntosh

Introduction

When I (Sarah) was a music therapist, I worked in long-term care with individuals in the middle to late stages of Alzheimer's disease. Their referral documents showed a fairly standard pattern: "nonverbal, nonambulatory, does not attend recreation programs, likes music." "Likes music" was how I wound up with a large caseload of clients and a long list of questions. With few exceptions, my clients *did* like music—so much so that the word *like* barely seemed adequate to describe what happened during our sessions: a smile blooming across a normally expressionless face, singing in voices and languages their loved ones hadn't heard in months or years, improvising with new and familiar instruments. This goes beyond liking and into something much deeper.

Playing and listening to music, no matter how simple the melody, is complicated from a brain perspective (see Williams and Sachs's chapter 11 in this volume for an excellent walkthrough). First, there's the sound itself. Sound hits the ears and gets converted into brain signals, where the brain figures out whether the input is music, speech, or something else and starts parsing the content: what does the sound mean? If you've heard the song before, you make predictions about what happens next, and you'll notice if there's an error (e.g., if the song has been edited for radio, if it's a live version that deviates from the album version). You might even experience memories related to that song if it's from a significant time in your life. If you're playing the music yourself, other brain networks are involved in physically operating the instrument and planning your next steps—while listening to the sound and rapidly correcting course if something goes wrong. There are many balls to juggle, yet most of us are able to do this effortlessly. How? Well, practice helps, but it's all thanks to an intricate system of brain networks.

This system of brain networks is established early in development and grows and changes as we age. Adaptation continues into adulthood, which is seen as individual

differences in cognitive aging and response to illness and injury. Successful prediction of how different individuals will respond to treatment for a stroke or progress through a neurodegenerative disease may benefit from understanding how these brain networks operate during real-world behavior. Music fits in nicely here, as it is broadly enjoyable, cognitively complex, and accessible to individuals with cognitive decline in a way that traditional text-based assessments are not. Music and music therapy have been shown to benefit individuals in long-term care (see Särkämö & Sihvonen, 2018), and by adapting tools from complex systems research, we can leverage music's complexity to capture the variability and richness of brain dynamics in aging.

Overview

In the following sections, we outline temporal and spatial concepts from complex systems research, introducing the space-time structure of the brain. We review how information is extracted from a complex system using multiscale measures and briefly discuss recent findings from studies across the human life span. We then expand this information to a manifold framework, showing how multiple configurations, or repertoires, can be active and lead to complex behavior. We also review the hidden states that are physiologically possible but accessed only with injury or illness and discuss this framework's utility in studying individual variability in aging using music, itself a complex system.

Complexity

The science of complexity covers a wide range of systems, from biology to the study of group behavior and social systems (Holland, 2014). The common characteristics of complex systems, such as nonlinearities and emergence, provide a better understanding of the similarities between systems and open the possibility of linking the complexity of one system with the complexity of another.

Perhaps one of the essential features of complex systems is their dependence on time. Complex systems are considered synonymous with dynamic systems: the system's characteristics depend on when it is observed. Previous work has demonstrated that the particular behavior of a system is dependent on its initial conditions. Even with identical core components, a slight variation in where the system begins can lead to a qualitatively different outcome as it evolves. This makes complex systems challenging to study because their behavior is hard to predict. With simple systems, in contrast, we can easily predict the outcome for a given set of inputs. We use the *simple* designation most often with linear systems, where we can estimate the output as a weighted

combination of the inputs. In complex systems, because of their nonlinearities, the best we can do is define a space over which a given set of initial conditions will lead to a distribution of potential outcomes.

The time aspect of complex systems plays out at another level, wherein the system's evolution has multiple timescales that can influence one another. Slow timescales usually act as a background over which faster timescales are expressed. Let's imagine a piece of music. The harmonic structure that makes up the tonality of the piece (whether it's major, minor, modal, or tonally ambiguous) relies on how individual notes are organized in time. Although individual chords can express tonality, how we understand the broader tonality of a piece is expressed over a slow timescale that relies on consistent harmonic patterns over time. Melody can then sit on top of the slow harmonic structure, shifting between consonance and dissonance with the underlying harmonic structure at a faster timescale without changing the piece's tonality.

In the brain, this temporal interplay is seen in the variation of signals that underlie cognitive function. For most operations during cognition, fast and slow processes can be seen in the changes in high and low frequencies, respectively, in brain signals. Sometimes lower frequencies dominate, acting as "carriers" for higher frequencies. The exchange of information through oscillations at different frequencies is thought to be the basis for communication in the brain (Buzsaki & Draguhn, 2004).

It is hard to discuss time dependence in complex systems without considering space. This is especially true in the brain, where we talk about networks of regions that interact with one another during different behaviors. These networks have a particular topology that spans a differing amount of space and therefore differing times. Brain regions that are connected over a long distance take more time to interact than regions that are close. This intersection of space and time is often referred to as the *space-time structure*, a widely used term in fields from quantum physics to biology. In the brain, the space-time structure nicely captures the notion that complex systems have an architecture that constrains but does not completely determine the system's emergent behavior from a process (Deco et al., 2011). Stated differently, the space-time structure constrains the range of what could happen, but what does happen is determined by the initial conditions.

The brain's space-time structure changes with maturation and aging. The connections between cells and regions change with experience. Long-range white matter connections become more effective insulators, enabling rapid signal propagation, while local connections are formed and pruned to support adaptive behavior. This process is referred to as the progression between *segregation* and *integration*. Segregation occurs when the local configuration of neurons in an area changes to become specialized for

particular types of information. A simple example is when areas connected along the auditory pathway become more specialized to segregate auditory information into parcels, such as pitch and timbre. However, the information needs to be integrated to ensure that the full percept is formed and that it can be integrated with other systems, such as the vision and motor systems, so that appropriate actions can be executed. Integration is supported through the white matter connections between regions. A complex system is one that shows an optimal balance between segregation and integration. When a system moves too far in either direction, complexity declines. Too much segregation allows incoming information to be broken down, but it cannot be integrated to drive the system forward. With too much integration, the system cannot adequately parse incoming information, and it tends to show the same response even with different information. This balance is vital for the adaptability of the brain. As information comes in, it can be appropriately parsed but also linked to potential responses. Stimulus-response mapping undergoes constant evaluation, and mappings can be updated to optimize adaptation. This is the hallmark of a complex *adaptive* system like the brain.

Information Processing in Space and Time

Because of the ever-present balance of segregation and integration, complex systems generate signals that are mixtures of processes across timescales. As a result, there tends to be more information in signals from complex systems than from simple linear systems. Indeed, complex systems can show a combination of entirely random noise mixed with activity from legitimate sources. The noise in complex systems is a benefit, as it provides the “kinetic energy” to drive the navigation of possible network configurations, but it is a curse in linear systems, as it obscures the input-output relationship (Faisal et al., 2008).

One way to assess the information content of a signal is to measure its *entropy*, which we define here as a measure of predictability. More predictable signals have low entropy, while signals that contain a mixture of scales have high entropy. However, this latter feature is a bit of a problem because signals that are only noise and signals that contain information may have similar levels of entropy. One solution takes advantage of the space-time structure of complex systems. Information may be available across multiple scales in a complex system, while noisy systems with random space-time structures have little information across scales. We used a metric called multiscale entropy (MSE; Costa et al., 2005) that measures entropy as a function of temporal scale. Entropy of the original signal is calculated; then the signal is successively down-sampled, and at each sample, entropy is calculated again. For a complex signal, entropy remains

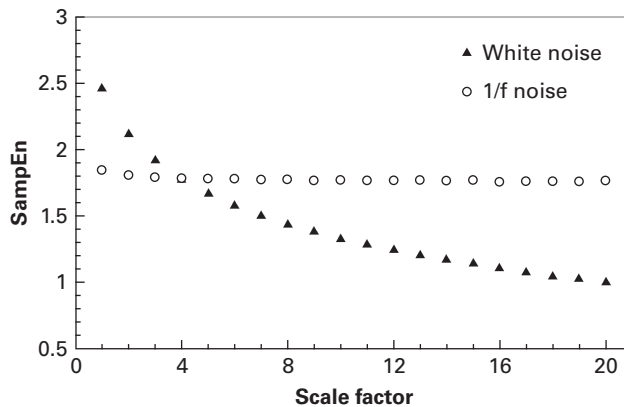


Figure 12.1

Example of MSE curves for two signals. The y-axis is entropy, and the x-axis is timescale. White noise has little information beyond the first few scales, and sample entropy (SampEn) drops. 1/f noise, which has dependencies between frequencies, has information across multiple scales, so sample entropy remains high across many timescales. Figure extracted from <https://archive.physionet.org/physiotools/mse/tutorial/node2.html>.

high for most down-sample levels, while entropy for a noisy signal declines as it gets progressively smoother. These observations can be depicted in an MSE curve that plots entropy by timescale (figure 12.1).

A second benefit of looking at information across scales of a complex system is that we can relate the timescale profile to determine whether there is a particular scale at which information is highest. We can then relate the shape to the space-time structure to identify the collection of networks with the highest information-processing potential. We have examined this relationship across maturation and aging to see whether the link between information and space-time changes and whether this relationship breaks down in the face of pathology such as dementia. This relationship between the space-time structure and information processing (see McIntosh, 2019) can be summarized as follows (see figure 12.2):

1. We can use healthy young adults as the reference point. Collectively, they show a gradual increase in entropy with a timescale that peaks at midrange and then declines slightly. In relation to the space-time structure, this means that information at fine scales (shorter timescales) would be lowest, with more information at medium timescales and then dropping at slower timescales.
2. Children (from infants to about ten years old) show a similar relative relationship across scales, but the overall level of entropy is lower.

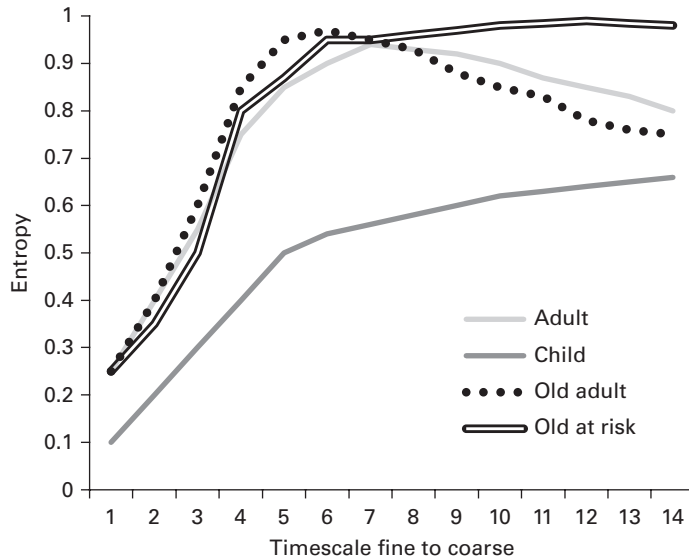


Figure 12.2

Schematic representation of the MSE curves measured from the brains of four age groups. The y-axis is entropy, and the x-axis is timescale.

3. Healthy older adults (fifty to eighty-five years) show relatively greater entropy at faster scales and less at slower scales. This pattern is associated with good cognitive status for the cohort.
4. Older adults at risk for cognitive decline show relatively less information at fine scales and more at coarse scales. This pattern can be seen before the overt expression of cognitive decline, suggesting that it may be prognostic.

We can further relate these observations to brain organization by stating the following:

1. The healthy adult brain shows optimal information processing at intermediate spatiotemporal scales.
2. Children show overall lower information processing than adults, which increases with maturation. This correlates nicely with the structural changes in development, where local processing capacity increases with neuronal pruning, complemented by increased myelin density that facilitates long-range interactions.
3. The healthy older adult brain shows optimal information integration at local spatiotemporal scales, with less integration at longer ranges.
4. Adults at risk for cognitive decline show lower information processing locally but more at longer ranges.

The details underlying these changes are not well known but are likely the result of both structural changes that occur across the life span and pathological changes that may affect local neural populations. These brain changes also occur in a rich environmental context, which opens the possibility that the particular patterns of information processing within the space-time structure reflect the intersection of biological and environmental factors.

Implications of a Complex Systems Framework for Music Neuroscience

If we accept that the brain has a rich spatiotemporal structure, we can assume that any emergent cognitive functions will show a complementary richness. This connection is captured in the notion that cognitive functions—or indeed, any function—should be considered processes rather than discrete states. The “state bias” is evident in the common practice of treating functions as static in neuroscience research. In part, this may reflect the fact that much of what happens across time in functions such as memory or attention is invisible to us, and an estimation of the function is reduced to point estimates, such as accuracy or reaction time. Much of music research follows this practice, but music’s temporal structure makes it perfect for relating to the brain’s concomitant temporal structure that evolves with music.

There is a challenge associated with linking the temporal structures of music and the brain. The phenomenology of music is an emergent feature of elements. Accounting for this emergence in the study of music and the brain could provide unique insights into how the emergent features of music interact with the emergent features of brain function. Past work has quantified patterns of behavioral responses to musical pitch (Krumhansl, 1990) and the neural correlates of harmonically rich music (Alluri et al., 2012), personally significant music (Salimpoor et al., 2011), improvisation (Limb & Braun, 2008), and social music making (Lindenberger et al., 2009; Müller et al., 2013; Sanger et al., 2012; Donnay et al., 2014). However, important information is lost by dividing music perception into discrete categories and a priori selecting circumscribed sets of brain regions known or theorized to respond to these categories. Such work has been fundamental to our understanding of music and the brain, but music is much more than sequences of tones, and the brain is much more than the firing of neurons.

One way to link the emergent features of music and the brain is to use metrics that are sensitive to the whole rather than the parts, such as multiscale entropy. We can characterize the complexity of music by measuring its entropy as a function of timescale. This is possible because music has a rich temporal structure. At finer timescales, information related to the acoustic or timbral properties of the sound is dominant, while properties related to structure (novelty, tonality, rhythm) are dominant at coarser

scales. The advantage of using MSE to measure complexity for both music and the brain is that we can now link these complexity metrics when someone listens to music.

We obtained electroencephalograms (EEGs) in young adults while they listened to short musical excerpts under two conditions (Carpentier et al., 2020). In one condition (Perceptual), the participants were asked to track the relative pitch and tempo of the music as it unfolded. In the second condition (Emotional), the participants were asked to track their relative changes in arousal and valence to a different set of music. In essence, the Perceptual task had participants focus on the physical characteristics of the music, while the Emotional task had them focus on how the music made them feel. We then measured MSE from the participants' brains and MSE from the music they were listening to and measured the geometric distance between the shape of the two MSE curves. The idea was that the closer the participants were tracking the music, the smaller the distance between the MSE curves.

This is what happened, and a bit more. Figure 12.3 compares the changes in distance between MSE curves for music and the brain in both the Emotional and Perceptual tasks in ten-second epochs. A higher "brain score" means that the distance between curves is greater. The results show that the distance for the Emotional task is greater than that for the Perceptual task. In addition, the MSE curves for the Emotional task

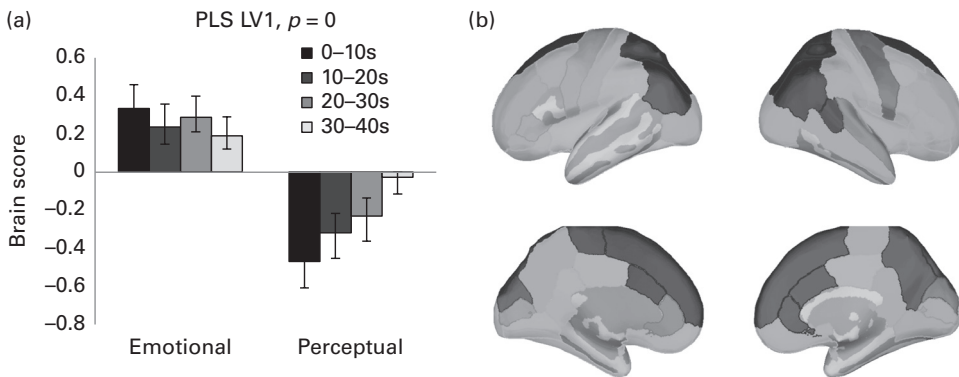


Figure 12.3

Analysis of the match between brain and music complexity. Higher scores mean more distance between brain complexity and music complexity. The bar graph in panel A shows the change in the match across ten-second epochs of music listening, where either subjective emotion (Emotional) or changes in pitch and tempo (Perceptual) are judged. Panel B shows the brain regions most strongly involved in this change, with the darkest colors indicating the most robust contribution. Many of these areas are part of the brain's default mode network, which is thought to be critical for integration with other brain networks.

are larger than those for the Perceptual task. This means that participants “added” extra information in their brains when listening to music and judging how they felt.

We also measured whether the distance of the MSE curves was related to the participants’ music listening behavior in general. Interestingly, we discovered that individuals with greater distances between music and brain MSE curves found music more rewarding in general, as assessed by the Barcelona Music Reward Questionnaire (Mas-Herrero et al., 2013). Basically, the more information a participant adds to the music signal as it courses through the brain, the more personally rewarding music is to that person.

This intersection of complexity in music and the brain opens a new avenue of exploration to determine how the individual features of a person’s brain operations relate to that person’s current experience. We can capture spatiotemporal brain patterns more explicitly using methods such as hidden Markov modeling (HMM; Vidaurre et al., 2016). This technique works by assuming that there are several hidden states—here, defined as either brain networks or features of music (see below)—whose activities vary across time as a process evolves. For the brain, one can envision different functional networks (e.g., auditory, motor, default mode) varying in engagement when listening to music. For music, one can express states in terms of the shifting prevalence of acoustic features (e.g., loudness, roughness) or structural features (e.g., modality, novelty) derived using music information retrieval (MIR) methods such as the MIR toolbox (Lartillot & Toivainen, 2007). In both cases, the critical output of HMM is how the states relate across time in terms of which states are more likely to follow one another.

We also applied HMM to both music and brain data (Faber & McIntosh, 2022). The brain states were divided among perpetual networks for monitoring the musical signal, goal-directed movement networks for operating the mouse tracker, and emotional or interoception networks for monitoring internal states and activation and deactivation states for the default mode network (DMN), which is ubiquitous during wakeful rest. We found that the emotional listening condition with a higher complexity score in the previous analysis now showed a repeating circuit of activity between brain states related to the deactivation of the DMN, cursor movement, decision making, and the processing of emotions tuned to structural features in the music. A similar circuit was present in the perceptual condition but tuned to acoustic features in the music, reinforcing the emergent nature of music listening. When analyzing functional connectivity states over time, we saw larger patterns of activity that weren’t captured by correlating the brain data to the music or behavioral features. These results also raised some interesting questions about how the brain employs repeating patterns of networks over time to generate complex behavior. How robust are these networks? Will they adapt with age and expertise, and what happens with aging and injury or illness?

Age Effects

The HMM approach has great potential to capture the changes in spatiotemporal flows in aging and dementia. There are few examples in the literature, but the work consistently shows that both the spatial pattern of brain networks and their temporal dependencies change in aging. One of the first studies to do so was by Cabral et al. (2017), using leading eigenvector decomposition analysis (LEIDA), which is comparable to HMM. The researchers analyzed functional magnetic resonance imaging (fMRI) scans in 120 subjects aged fifty years or older obtained while they were resting in the

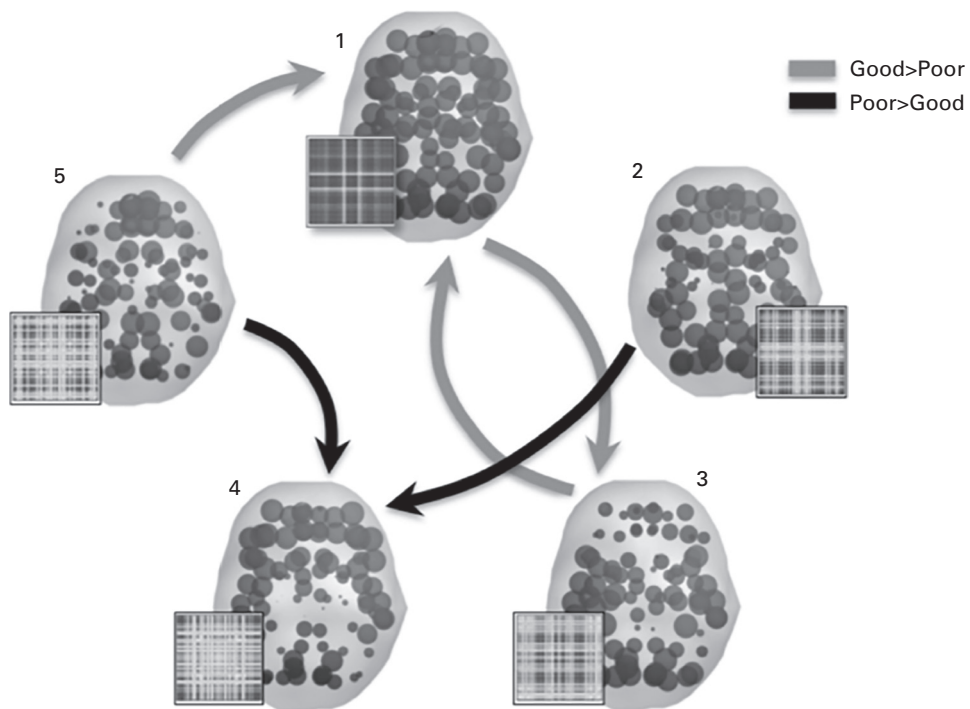


Figure 12.4

Summary of resting-state fMRI data from older adults using LEIDA. The five common states are numbered 1–5, and nodes in each state are displayed as colored balls; the color map shows the degree of correlation between nodes, with darker shades indicating a higher correlation. Arrows connecting the states indicate the paths where the transitional probability between those states differed in relation to cognitive status (gray=stronger transitional probability in persons with relatively good cognitive performance, black=stronger transitional probability in persons with relatively poor cognitive performance). (Figure excerpted from Cabral et al., 2017.)

scanner (resting state). The participants were divided into two groups based on neuropsychological memory and attention.

LEIDA identified five spatial patterns corresponding to distinct functional network states (Figure 12.4). These networks had temporal relationships that differed between groups, indicated by the transitional probabilities of moving between states. Thus, although the states may be relatively stable in aging, the way they interact across time is not. Complementary work from Battaglia et al. (2020) studied a broader age range (eighteen to seventy years). These investigators focused on the temporal switching of networks, specifically examining the speed and number of switches in relation to aging and cognitive status. One major finding was that there is less network switching across age. This does not mean it stops, but rather the switches become less frequent. A second outcome was that, among the older subjects, faster pattern switches related to better cognitive status. These two examples underscore that the key to understanding the aging brain involves more than determining whether certain brain regions are intact; the broader patterns of region interaction across the brain and over time are important as well.

The same motivation can prompt us to apply spatiotemporal analyses like LEIDA or HMM to neurodegenerative disorders in aging (Sourty et al., 2016). In that case, the emphasis would be on differentiating changes in the spatiotemporal structure related to neurodegeneration itself and to aging and analyzing the potential interaction of the two processes. Moreover, given the disparity across individuals in response to the degenerative process, a focus on individual modeling is critical (Botha et al., 2020).

To make progress, however, we need to go beyond simply characterizing differences in the brain and move toward linking the spatiotemporal flows in the brain with the concurrent flows in behavior. In our initial example, it is possible to envision that ongoing flows in the brain of a person with dementia move as that person listens to music, and the music's familiarity takes that individual to a vivid moment in his or her history. The music study in which HMM was applied to the brain and to music is a good example of how we can design studies that better link the brain and music experience.

An emerging theory of complex systems focuses on brain and behavior, emphasizing their mutual dependency. This theory, termed structured flows on manifolds (SFM), posits that behavior can be appreciated as the expression of flows bounded by manifolds (Perdikis et al., 2011a, 2011b; Pillai & Jirsa, 2017). Flows can be a series of movements, the perception of a series of sounds that combine into music, or the transition between brain states that link movement and perception. The manifold provides the constraints for which flows can be accessed—essentially, the rules. There can be variations in flows that depend on initial conditions and the inherent randomness of nonlinear systems, but the SFM approach provides a comprehensive framework to connect brain and

behavior processes in terms of the available potential actions (flows). This is an important point because most brain theories are derived only from what a system does when it is observed. SFM differs, in that it focuses on what the system did at a given time (the actual flow), why that flow happened (the manifold that dictates the rules), but also what *could have* happened (the potential flows). This potentiality is essential for complex adaptive systems and can bring a new perspective on the brain's capacity to process information (McIntosh & Jirsa, 2019).

The SFM framework also provides a different perspective on brain changes in neurodegeneration. With progressive decline, the preferred navigation of flow on manifolds may be unavailable, but there may be alternative routes through different pathways. This hypothesis is exciting in terms of providing a potential therapeutic target to help maintain or recover some behaviors compromised by degeneration. If the degenerative process can be detected early, characterization of the manifold architecture for that individual can guide interventions to develop alternative flows to support equivalent behaviors. Such characterization is becoming possible with TheVirtualBrain neuroinformatics platform (Ritter et al., 2013; Sanz Leon et al., 2013), which can simulate a person's entire brain from structural and functional brain imaging data. The simulation then becomes a virtual laboratory to explore the SFM architecture for that person. If flows are compromised, manifold estimation may also yield clues on how to reintegrate brain networks, and simulations can be done to test the potential for actual intervention.

Music uniquely engenders multiple systems in the brain. Perceptual and motor networks are the usual suspects, but linguistic, social, and emotional components are indivisible from the musical experience. The social aspect links with the listener's personal history via personal memories. Understanding how we maintain our connection to music with the onset of neurodegeneration requires extensive foundational knowledge on the nature of the brain, music, and aging. How does the brain process music from a purely perceptual standpoint? How do emotion, preference, and familiarity factor in? What patterns describe an individual's brain activity in response to music, and how do we reconcile individual differences? How do these patterns change with age and neurodegeneration? Why does one individual with Alzheimer's disease still sing his or her favorite song while another does not? By applying the complex systems framework, we can start addressing some of these questions, leading to a greater understanding of the richness of individual brain health across the adult life span.

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