SCIENCE AND CULTURE

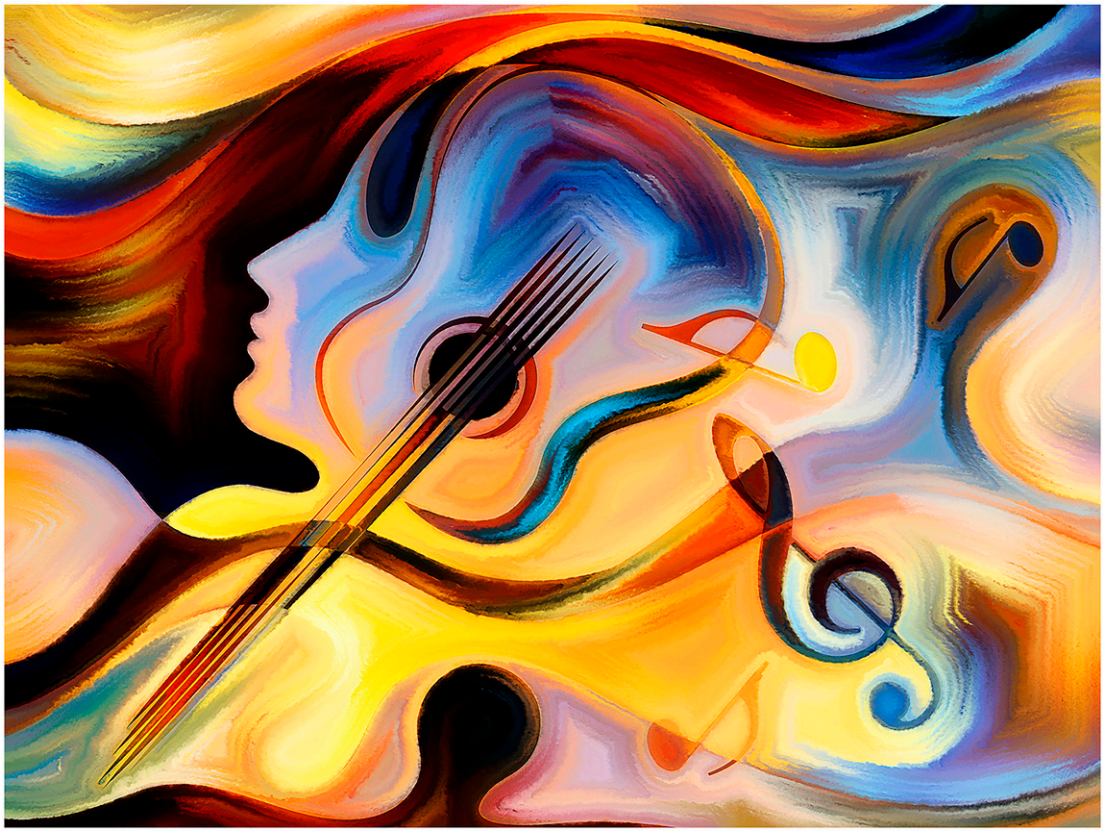
# At the nexus of music and medicine, some see treatments for disease

**Amy McDermott,** *Science Writer*

When physician Babar Khan started studying delirium seven years ago, he set out to find a drug that could sooth the agitation, inattention, and hallucinations that characterize the disorder. Delirium is common in the intensive care units (ICUs) where Khan works, most recently as an ICU physician at Indiana University School of Medicine and a researcher at Regenstrief Institute, both in Indianapolis. Some 70–80% of ventilated patients in the ICU experience episodes of delirium that not only prolong their stay in hospital but can also lead to long-term cognitive decline.

In the mid-2000s, Khan led two antipsychotic drug trials, neither of which worked for delirium. "So I started looking into more holistic interventions," he says. He recalled seeing some evidence, drawn from assessments of anxiety and sedative exposure in hospital patients, suggesting that music can not only ease anxiety in the ICU but can help with pain management (1). The music-related findings would spur Khan to start investigating music as an alternative to pharmaceuticals. He recently co-led a 2020 pilot trial using music to alleviate delirium in mechanically ventilated ICU patients. Encouragingly, he found that relaxing, slow-tempo classical music reduced patients' number of delirium days (2).

That study is one of many new projects seeking evidence for music as a medical therapy. Cultures have used music in healing for centuries. Although the



**Neurologists, cognitive neuroscientists, and clinicians are coming together to study the therapeutic potential of music. Image credit: Shutterstock/agsandrew.**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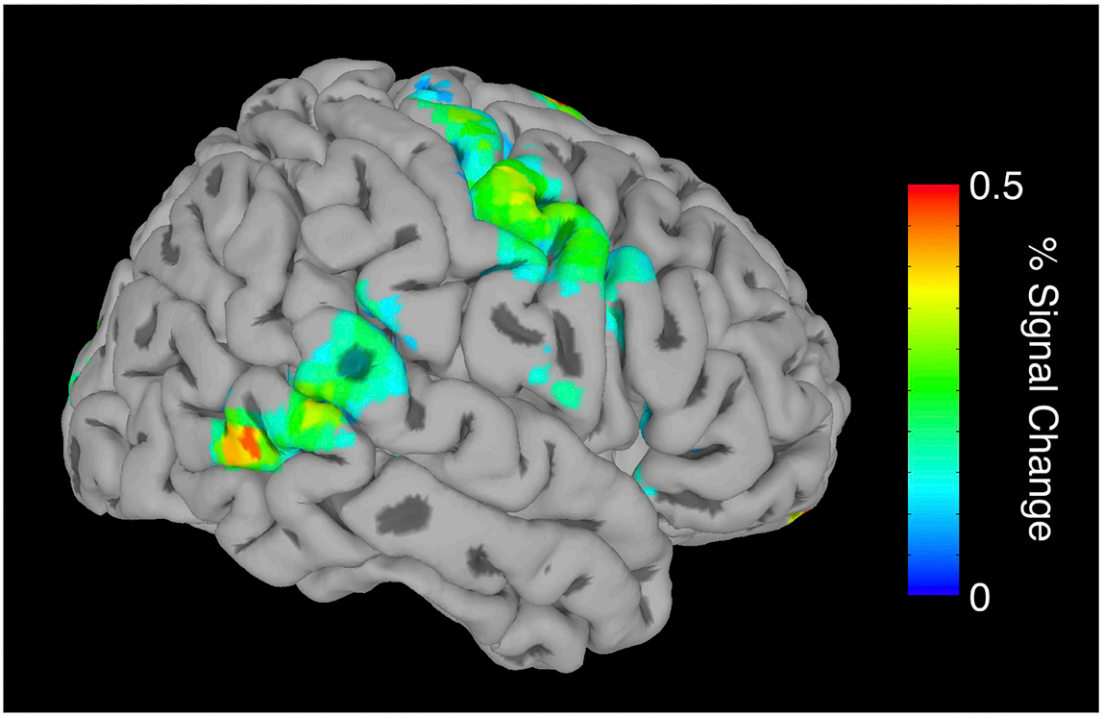


**As part of an NIH-funded experiment, soprano Renée Fleming underwent a functional magnetic resonance imaging (fMRI) scan of her brain in 2017. The scan highlights areas of increased signal (commonly interpreted as increased brain activity) when Fleming imagined singing while inside the fMRI scanner. Learning more about music's interactions with the brain could lead to new and better medical therapies. Image credit: National Institutes of Health/David Jangraw.**

evidence is still limited, a growing body of research offers increasing promise for music's health benefits. And the field is seeing a new injection of funding. Based on his pilot trial, Khan secured funding for a confirmatory trial through the Sound Health initiative, a partnership between the the National Institutes of Health (NIH) and the Washington, DC-based John F. Kennedy Center for the Performing Arts, in association with the National Endowment for the Arts, to expand research on music's impact on the brain and body, as well as its therapeutic potential. In 2019, Sound Health awarded $20 million in research grants over a five-year period, with more to come. So far, growing evidence points to a range of musical medical benefits for ailments from stroke to Parkinson's.

"There was a while where it felt like, every week there was a new study," says Tom Cheever, who coordinates NIH activities related to the partnership. "There's sufficient data coming out," he says, "that it's worth digging in further."

## Fine Tuning

The intersection of music and medicine spans disciplines from neuroscience to clinical research. Indeed, music has been part of medicine, in one way or another, from the earliest efforts to heal the sick. "Arts and health were very much interwoven from the beginning," writes University College London, England psychobiologist Daisy Fancourt in her 2017 book *Arts in Health* (3). Some 35,000 years ago, she notes, around the time that humans began painting animal figures in ochre and black on cave walls, shamans used bone flutes and animal skin drums in healing and funerary rituals. Fast forward to the 20th century, and musicians took up the mantle of healers after the First World War by playing for wounded soldiers in veteran's hospitals (4). Anecdotally, the soldiers responded so well that hospitals brought in musicians; the National Association for Music in Hospitals was born in 1926, according to the American Music Therapy Association. In the decades that followed, hospital musicians developed an accreditation system and became known as music therapists, as their work became increasingly tailored to patients experiencing a range of disorders. Today, music therapists work in settings from hospitals, to outpatient clinics, to nursing homes, where they are typically members of a patient's interdisciplinary treatment team along with medical doctors, neurologists, and psychologists.

Music therapists often publish observational analyses of qualitative patient responses to different therapeutic methods. For instance, one 2020 metasynthesis in the *Journal of Music Therapy* reviewed participants' qualitative experiences of guided music therapy while using psychedelics. Looking across 10 studies, the 2020 article concluded that patients found music both transformative and integral to their recovery (5).

Although music therapy is anecdotally effective, it's also been strongly criticized as being subjective, says cognitive neuroscientist Teppo Särkämö, at the University of Helsinki, in Finland. Much of the research in the 1980s, '90s, and early 2000s involved clinical trials that had methodological issues, including poor

experimental design, lack of randomization or blinding, and small sample sizes. In short, some music therapy research displayed "all the flaws you can imagine in clinical research," Särkämö says. In the most egregious cases, the same individual designed the study, delivered the intervention to patients, and analyzed the results. In properly blinded trials, the researchers analyzing the results would have no idea which patients received which treatment, so as to avoid bias. "That's one of the major issues of course," Särkämö says.

## Playing the Brain

In the last 15 years, as labs worldwide have studied how the brain processes music, some neurologists and cognitive neuroscientists started to focus on the potential of music to treat neurological disorders. As these neuroscientists entered a field once dominated by music therapists, newer trials have become more rigorously designed, Särkämö says. But these studies are "still a work in progress in many cases," he notes, because trials are still too few and too small to unequivocally demonstrate the effects of music intervention.

Cognitive neuropsychologist Simone Dalla Bella is among the researchers pursuing rigorous investigation of the therapeutic effects of music. Dalla Bella, codirector of the BRAMS Laboratory at the University of Montreal and at McGill University in Canada, investigates the cognitive and brain mechanisms underlying how we perceive music and how humans react to music through movement. His focus is patients with rhythm disorders, such as Parkinson's disease. Since the 1940s, clinicians have noted that walking to the rhythm of a metronome or music can help steady the gate of some Parkinson's patients, whose small, wobbly steps increase the risk of falling. But the mechanisms underlying this rhythm phenomenon are not well known.

Dalla Bella coauthored a 2017 study finding that simple rhythm tests, using finger tapping, can predict which patients will benefit from the metronome walking treatment (6). The study began with 14 patients with Parkinson's disease and an impaired ability to walk. First, before treatment, the coauthors assessed each patient's ability to perceive rhythm by asking them to tap their finger to the beat of music, walk to the beat of music, and synchronize their footfalls with the beat of music. Next, each patient underwent one month of therapy, in which they walked to the rhythm of a German folk song for 30 minutes, three times per week. The researchers measured each patient's walking speed and step size, before and immediately after the intervention, and again one month after the end of treatment.

The team found that, on average, the patients' walking patterns improved, their steps became longer, and they could walk faster and more normally after the intervention. However, not every patient improved. And when the researchers went back to the tests of rhythmic ability given before the treatment, they found that those patients who could tap to the beat of the music had improved the most in walking.

The findings hint at one reason why some patients benefit from music. Before this study, there were several competing hypotheses for how Parkinson's might disrupt normal rhythmic walking. The classical neurophysiological explanation of Parkinson's, Dalla Bella explains, is that the disease impairs the basal ganglia, a system of neural circuitry deep in the brain (7). The basal ganglia, in concert with a complex network including the cerebellum and cortical areas, normally regulate a person's sense of rhythm. Damaged basal ganglia may lose their ability to internally regulate rhythm, even while they retain some residual responsiveness to outside audio stimulation. Hence, music could, Dalla Bella and others speculate, jumpstart the ganglia to reactivate their rhythm-keeping function, in some cases restoring normal gait.

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Dalla Bella's study supports this hypothesis with the finding that patients who benefitted the most from the therapy were those who had some spared rhythmic ability, even before the experiment. That would suggest that although the basal ganglia were damaged, they were not so badly impaired that the circuitry couldn't be activated by outside stimulation. Perhaps patients who did not benefit from the therapy had ganglia that were too damaged from the disease, he adds. The cerebellum and other brain areas involved in rhythm processing may also play a role, he adds. Dalla Bella's research group next plans to follow up with neuroimaging to confirm which brain networks were engaged before and after the intervention. This would be the ultimate evidence to show whether residual or spared mechanisms are involved, he says.

Music may ease the symptoms of other neurological diseases as well. In a recent unpublished pilot trial likely to come out early next year, clinician scientist Gottfried Schlaug, at the University of Massachusetts Medical School, Baystate Medical Center in Springfield, tested whether a form of singing called melodic intonation therapy helped patients recover after a stroke on the left side of the brain. The blood clot damaged a region of the brain responsible for speech and vocal–motor operations. Patients sang simple phrases, such as "I am hungry," in a pattern of alternating high and low pitches, while simultaneously tapping to the rhythm with their unimpaired left hand. Compared with a control treatment (an alternative form of speech therapy) and no treatment, the pilot study found that the melodic intonation therapy effectively improved patients' ability to speak. Functional magnetic resonance imaging, he says, also showed dramatic changes to the right side of the brain

after repeated therapy sessions. These changes included increased activity and connectivity between right brain regions involved in vocal–motor or speech–motor functions. "This means they were not just activated more after therapy, but they also communicated more," Schlaug says. The imaging also showed an increase in grey matter in some regions of the right brain after therapy, he says, which suggests that, with practice, the right brain speech centers built up more neurons and support cells.

Schlaug's study is one of a small but growing number of clinical trials. Today, Särkämö estimates that there are some 60 ongoing clinical trials for neurological populations worldwide. Trial sizes vary, but one ongoing challenge is recruiting enough patients to estimate the strength of music's effects, Schlaug says. Hence, although there may be growing interest in music and medicine, rigorous clinical evidence "is still very weak," he notes. Many music intervention therapies were developed by music therapists in the days before well-controlled studies, "completely independent of the neuroscience," he adds. "And now we're trying to put them together."

## Finding the Key

Khan's 2020 delirium work is another example of a growing number of clinical trials, which are still typically small. Each of the 52 patients in this case had undergone mechanical ventilation in the ICU for about a day and then were assigned to a control (no music) or one of three treatment groups: listening to personalized playlists based on their music taste, generalized relaxing music chosen by a music therapist, or an audiobook such as *Harry Potter and the Chamber of Secrets*. Regardless of their treatment group, every patient listened for two hour-long sessions a day for one week. The researchers assessed patients daily to evaluate delirium, anxiety, and pain, for up to seven days. Eighty percent of the patients said that they enjoyed listening to the music. And among the treatment groups, general relaxing music resulted in the most delirium-free days (three, on average) and lowest delirium severity on a standardized seven-item scale.

This and many other new studies are bringing music and health to the forefront of funders' attention, Khan says. Although most studies are small, the largest-ever music intervention trial is now ongoing. Called Music Interventions for Dementia and Depression in Elderly Care (MIDDEL), it involves an estimated 1,000 patients across multiple European countries and Australia. The trial compares the effects of several music interventions on dementia and depression in residents of elder care facilities, age 65 or older.

With this growing knowledge base, "the time was right to bring neuroscientists and fundamental researchers together with musicians and music therapists." This is one goal of the Sound Health initiative, says Cheever. He acknowledges that many studies have been small and not always sufficiently controlled, and that significant work remains to be done. For now, notes Cheever, the NIH aims to provide the preliminary funding to build a strong evidence base to justify future larger trials. The growing number of anecdotes, case studies, and small studies prompted the investment.

Although $20 million over the first five years won't fund huge clinical trials that typically cost tens of millions of dollars each, the money should help build a stronger evidence base, says Schlaug. Currently, the NIH is supporting 15 projects and plans to support more, Cheever says. "My hope for the future," he adds, "is that a physician's tool box would have drugs, biologics, devices—and then music intervention might be one in there."


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