Music-based interventions in neurological rehabilitation

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During the past ten years, an increasing number of controlled studies have assessed the potential rehabilitative effects of music-based interventions, such as music listening, singing, or playing an instrument, in several neurological diseases. Although the number of studies and extent of available evidence is greatest in stroke and dementia, there is also evidence for the effects of music-based interventions on supporting cognition, motor function, or emotional wellbeing in people with Parkinson's disease, epilepsy, or multiple sclerosis. Music-based interventions can affect divergent functions such as motor performance, speech, or cognition in these patient groups. However, the psychological effects and neurobiological mechanisms underlying the effects of music interventions are likely to share common neural systems for reward, arousal, affect regulation, learning, and activity-driven plasticity. Although further controlled studies are needed to establish the efficacy of music in neurological recovery, music-based interventions are emerging as promising rehabilitation strategies.

Introduction

The world's population is ageing rapidly and the number of people with severe age-related brain diseases is increasing.[1] More than 80% of the heavy economic burden of chronic brain diseases is due to costs other than acute treatment and care.[2,3] This burden has raised the need to pursue new cost-effective, easily applicable rehabilitation strategies, both independent of and complementary to traditional methods such as physiotherapy, occupational therapy, and speech therapy. Since neurogenesis in the adult brain has no known clinically meaningful effect on brain recovery, functional restoration relies upon the ability of spared neurons to compensate for lost function by growing neurites and forming new synapses to rebuild and remodel the injured networks.[4–8] This functional restoration is thought to be achieved in traditional rehabilitation strategies by targeted training of the weakened function.[9–12] An alternative strategy is to increase the overall level of brain activity through sensory and cognitive stimulation.[13]

Music listening improves neuronal connectivity in specific brain regions of healthy participants,[14–17] and musical activities, such as playing an instrument, promote neural plasticity and induce grey and white matter changes in multiple brain regions, especially frontotemporal areas.[18–20] Music listening was efficacious in the recovery of postoperative patients who had various types of major surgery, as measured by several outcomes such as levels of pain and anxiety, use of analgesics, and patient satisfaction,[21] suggesting that music might also enhance neurological rehabilitation.

Formal music-based intervention can be defined as active intervention (eg, creating music, playing an instrument, singing, or musical improvisation) or receptive intervention (eg, music listening) that is administered by a credentialed music therapist (panel). Although a Cochrane review evaluated the effect of music intervention on recovery of acquired brain injury,[22] a comprehensive overview of music-related interventions in the rehabilitation of the major neurological diseases, including degenerative ones, is needed. In this Review, we appraise the randomised controlled trials investigating the effects of music-based interventions in the rehabilitation of patients with stroke, dementia, Parkinson's disease, epilepsy, or multiple sclerosis. For comparison of the studies included, we define the effect sizes of improvements in the specified outcome as small (Cohen's $d \geq 0 \cdot 2$), medium ($d \geq 0 \cdot 5$), or large ($d \geq 0 \cdot 8$). Effect size was defined as the mean change in outcome before and after treatment in the treatment group minus the mean pre–post change in the control group, divided by the pooled pretest standard deviation.

Music-based interventions for stroke

Stroke is one of the leading causes of long-term disability worldwide.[23] Of the major neurological disorders, the strongest evidence for efficacy of music-based interventions has been reported for stroke. We identified 16 randomised controlled trials that used music as an add-on therapy for stroke-related neurological and neuropsychiatric disturbances (table).[24–39] The assessed outcomes included motor functions, such as gait and upper extremity function;[24,25,27,30,31,34–39] language functions;[26,28,29] cognitive functions, such as memory and attention;[28,33] mood;[28,33,36] and quality of life.[30,36] These outcomes were measured with various standard motor tests (eg, Fugl-Meyer Assessment, the Box and Blocks Test, Berg Balance Scale, and Nine-Hole Peg Test), clinical neuropsychological assessments (eg, CogniSpeed, Revised Wechsler Memory Scale), standard language function assessments (eg, Boston Diagnostic Aphasia Examination), and questionnaires (eg, Stroke Impact Scale, Profile of Mood States, and Stroke and Aphasia Quality of Life Scale-39). Additionally, computer-based movement analyses,[30,35,38,39] MRI analysis,[28,31,33] magnetoencephalography,[31] or electro-encephalography[34] were used to assess motor performance and neuroplasticity. Metronome-like rhythmic stimulus was used in five studies of stroke-related motor paresis.[30,31,36,37,38] The participants' favourite music, selected through interview, was used in three studies,[28,32,33] although the genres of favourite music were not reported. Three studies used children's songs and folk songs.[24,34,35] Five studies involved a trained music therapist.[26–28,32,33]

Effects on motor symptoms

Hemiparesis is the most common consequence of stroke, affecting over 70% of patients.[66] Eight studies reported enhanced motor recovery when patients who had a stroke were rehabilitated with a music-based intervention.[25,27,30,34–38] Four of these studies investigated the use of rhythmic auditory stimulation (panel) in gait training and all four found the intervention to improve gait parameters more than gait training without any musical support.[30,37–39] Across studies, significant improvements were observed in gait velocity (d=0·46–2·13), stride length (d=0·49–1·50), length of foot contact to surface (d=0·40), cadence (d=0·02–1·82), and symmetry (d=0·52–0·83) after 3–6 weeks of rhythmic auditory stimulation compared with conventional training without rhythmic auditory stimulation (table).[37–39] There were similar findings when intensive gait training with rhythmic auditory stimulation was investigated with respect to postural control and gait performance in patients with chronic stroke.[30] In one study,[30] over the course of 6 weeks of intervention, the rhythmic auditory stimulation group improved in balance, gait velocity, cadence, stride length, and double-support period on the affected side. In another study,[36] when rhythmic auditory stimulation was used in the form of combining rhythmic music with movement therapy, patients who had a stroke showed improved ankle (d=0·61) and arm movement (d=0·99) after 8 weeks of intervention. One study compared bilateral arm training with rhythmic auditory stimulation to dose-matched therapeutic exercises, but there were no significant differences between the groups.[31] Numerically, rhythmic auditory stimulation done by a music therapist (compared to control) resulted in greater improvement compared with stimulation by a non-music therapist (compared to control).[22]

Music-supported therapy (panel) was efficacious in rehabilitating arm paresis after stroke in five randomised controlled trials.[24,25,27,34,35] 3 weeks of music-supported therapy improved motor skills in the patient's paretic arm significantly more than conventional physiotherapy, an effect shown by several validated clinical tests (Cohen's d=0·24–0·69).[34,35] The effect was accompanied by improved cortical connectivity and increased activation of the motor cortex.[34] The improvement in motor skills observed seemed to be specifically caused by music rather than by motor training, since patients practicing with mute instruments showed less improvement than the music group.[27]

One study[25] used movement sonification therapy, a recent development in music-supported therapy in which gross movement is transformed into sound, providing continuous feedback, substituting for deficits in proprioception. Movement sonification therapy reduced joint pain (Cohen's d=1·96) and improved smoothness of movement (d=1·16) more than movement therapy without sound. Delayed auditory feedback in music-supported therapy could be as effective as traditional immediate auditory feedback therapy.[24] Although both rhythmic auditory stimulation and music-supported therapy involve auditory-motor coupling, incorporating music stimulus might result in enhancement of the therapeutic effect because of the personal motivational value of music. Internal synchronisation, based on musical memory, generates the expectation of consecutive sounds of a familiar song, and provides precise mental timing feedback for movement, thus supporting the patient's impaired proprioception.

Panel: Definitions of key terms

Music-based intervention
Refers to all experimental protocols that use music in various forms to study its therapeutic effects.

Music therapy
Music-based interventions delivered in a clinical setting by a credentialed music therapist that use various musical elements (eg, singing, or creating, moving to, or listening to music).

Music medicine
Various types of music-based interventions delivered by health-care professionals. The interventions have health-promoting goals, but often do not have the therapeutic relationship and reciprocal musical interaction that are characteristic of music therapy.

Rhythmic auditory stimulation
Neurological music therapy technique used in the rehabilitation of movements that are naturally rhythmic (eg, gait). In rhythmic auditory stimulation, a series of auditory stimuli are presented at a fixed rhythm, and movements are synchronised (entrained) to the rhythm.

Music-supported therapy
Music-based intervention developed for motor rehabilitation of stroke. In music-supported therapy, gross and fine movements of the hemiparetic upper extremity are trained through playing musical instruments (eg, drums, keyboard).

Melodic intonation therapy
Singing-based intervention developed for rehabilitation of people with non-fluent aphasia. In melodic intonation therapy, the intonation of speech is expressed as low and high pitches. Production of linguistic phrases is achieved by training with a music therapist, first by intoning (singing) them at a slow pace and steady rhythm supported by tapping, then following a hierarchy of steps that eventually transforms communication from singing to speech. Training starts with singing two-syllable words and proceeds gradually to phrases.

Effects on aphasia

Aphasia affects approximately 30% of patients who have had a stroke.[66] In two randomised controlled trials, active music therapy improved the speech of people with chronic aphasia.[26,29] In one study, melodic intonation therapy (panel),[67] a singing-based speech therapy designed for non-fluent people with aphasia, was given to 10 of 17 people with subacute aphasia.[29] In this study, melodic intonation therapy improved the patient's daily life communication (Cohen's d=0·76) and object naming (d=1·73) significantly more than those outcomes in the control group, which received other types of language rehabilitation.[29] Music-related speech therapy, particularly melodic intonation therapy, is conceptually elegant and music therapy interventions might be more effective in aphasia than speech training without music.[22]

Effects on cognitive and emotional deficits

Deficits in cognitive functions (eg, memory, attention, executive function) and mood (eg, depression) affect approximately 30–50% of patients who have experienced a stroke.[68,69] In one randomised controlled trial, 1 h daily listening to a participant's favourite music, selected with the help of a music therapist, and continued during the first 2 months after stroke, enhanced cognitive recovery.[33] In a 6-month follow-up, the music group still showed significant improvements in performance of tasks measuring verbal memory (Cohen's *d*=0·88) and focused attention (*d*=0·92), compared with a control intervention (audiobook listening) or standard care.[33] Compared with standard care, music listening was also associated with less depression (*d*=0·77) and confusion (*d*=0·72; figure 1A).[33] The cognitive gains measured after music

	Studies (n)	Partici-pants (n)	Music therapist involved	Blinding	Primary outcome	Overall duration of intervention	Main results
Stroke							
MST *vs* MST with delayed sound[24]	1	34	No	Single	Hand movement	5 h in 4 weeks	No significant difference between the groups.
Sonificated movement *vs* movement without sound[25]	1	25	No	No	Gross motor function	10 days	Sonification therapy reduced joint pain (p<0·05, *d*=1·96) and improved movement smoothness (p=0·04, *d*=1·16).
Singing, playing instruments, improvisation *vs* speech therapy[26]	1	20	Yes	No	Speech parameters in people with chronic aphasia	22·5–37·5 h in 15 weeks	Music therapy improved spontaneous speech (p=0·020, *d*=0·35).
MST *vs* playing mute instruments[27]	1	33	Yes	No	Upper-limb motor function	20 sessions in 4 weeks	MST improved motor functions (p=0·039).
Favourite music *vs* standard care[28]	1	49	Yes	Single	Grey matter changes associated with cognitive improvement	60 h in 8 weeks	Music listening increased grey-matter volume in frontal areas, limbic areas, and right ventral striatum. Reorganisation in the frontal areas correlated with enhanced recovery of verbal memory, focused attention, and language skills, whereas the limbic area reorganisation correlated with reduced negative mood.
Melodic intonation therapy *vs* other language intervention[29]	1	27	No	Single	Speech parameters in non-fluent aphasics	30 h in 6 weeks	Melodic intonation therapy improved daily life communication (*d*=0·76) and object naming (*d*=1·73).
RAS *vs* intensive gait training[30]	1	20	··	No	Postural control and gait performance	15 h in 6 weeks	RAS improved balance, gait velocity, cadence, stride length, and double support period on the affected side, and improved score on stroke-specific quality-of-life scale.
Bilateral arm training with rhythmic auditory cueing *vs* normal exercise[31]	1	92	No	Single	Functional reorganisation and outcome	18 h in 6 weeks	There were no significant differences between the groups.
Favourite music and audiobook listening *vs* standard care[32,33]	2	54	Yes	Single	Auditory sensory memory;[32] cognitive functions and mood[33]	60 h in 8 weeks	Listening to music and speech after neural damage can induce long-term plastic changes in early sensory processing;[32] music listening improved verbal memory (p=0·002, *d*=0·88) and focused attention (p=0·012, *d*=0·92) compared with the audiobook and control groups. Music group also had less depression (p=0·031, *d*=0·77) and confusion (p=0·045, *d*=0·72) than the control group.[33]
Children's music and folk songs *vs* conventional therapy[34,35]	2	62;[34] 40[35]	No	No	Neuroplasticity and motor recovery;[34] motor recovery[35]	7·5 h in 3 weeks	MST improved motor skills showed by action research arm test score (p<0·001, *d*=0·32), arm paresis score (p<0·05, *d*=0·46), Box and Blocks test (p<0·001, *d*=0·43), and Nine-Hole Peg Test (p<0·05, *d*=0·32);[34] music group improved in speed, precision, smoothness of movements, and motor control in everyday activities evaluated by action research arm test (p<0·001, *d*=0·36), arm paresis score (p<0·05, *d*=0·42), Box and Blocks test (p<0·001, *d*=0·69), and Nine-Hole Peg test (p<0·05, *d*=0·24).[35]
RAS *vs* referral information[36]	1	33	No	No	Upper and lower limb mobility, mood, interpersonal relationships, and quality of life	16 h in 8 weeks	RAS improved range of ankle extension (p=0·018, *d*=0·61) and arm flexibility up (p=0·001, *d*=0·99) and down (p=0·008, *d*=0·62), mood (p=0·017, *d*=0·03), and increased frequency and quality of interpersonal relationships (p=0·003, *d*=0·96).
RAS *vs* neurodevelopmental therapy[37]	1	78	No	Single	Gait parameters	7·5 h in 3 weeks	RAS improved velocity (p=0·006, *d*=2·13), stride length (p<0·001, *d*=1·50), cadence (p<0·001, *d*=1·82), and symmetry (p=0·049, *d*=0·83).
RAS *vs* gait training without musical feedback[38]	1	23	No	No	Gait parameters	5 h in 3 weeks	RAS improved gait velocity (p=0·008, *d*=0·46), stride length (p=0·009, *d*=0·49), cadence (p=0·045, *d*=0·02), symmetry (p=0·008, *d*=0·55), and heel–toe distance (p=0·006, *d*=0·40).
RAS *vs* physical therapy[39]	1	20	No	Single	Gait parameters	30 h in 6 weeks	RAS improved gait velocity (*d*=1·45), stride length (*d*=0·93), symmetry (*d*=0·52), and cadence (*d*=0·44).

(Table continues on next page)

listening were associated with enhanced auditory memory-related function in temporal brain areas[32] and increased grey matter volume in prefrontal regions that had not been affected by the stroke[28] (figure 1B, 1C). Reduction in negative mood after music listening was associated with increased grey matter volume in limbic

	Studies (n)	Partici-pants (n)	Music therapist involved	Blinding	Primary outcome	Overall duration of intervention	Main results
(Continued from previous page)							
Dementia							
Multisensory stimulation *vs* music listening[40]	1	18	No	No	Neuropsychiatric symptoms and cognition	16 h in 16 weeks	Multisensory stimulation showed positive effects on anxiety symptoms and dementia severity that were not observed in the music listening group.
Music listening *vs* singing *vs* standard care[41–43]	3	83	Yes	Single	Emotional parameters;[41] clinical, demographic, and musical background factors influencing the cognitive and emotional efficacy of caregiver-implemented musical activities;[42] quality of life, mood, and cognition[43]	15 h in 10 weeks	Both music listening and singing groups improved in behavioural disturbances (p=0·04, *d*=0·42) and physical signs (p=0·008, *d*=0·52) more than the control group. Effects not present 6 months after the intervention;[41] singing was beneficial, especially in improving working memory in people with mild dementia and in maintaining executive function and orientation in young people with dementia. Music listening was beneficial in supporting general cognition, working memory, and quality of life, especially in people with moderate dementia not caused by Alzheimer's disease who were in institutional care. Both music interventions alleviated depression, especially in people with mild dementia and Alzheimer's disease. The musical background of people with dementia did not influence the efficacy of the music interventions;[42] music listening improved the patients' mood (p=0·001, *d*=0·80), orientation (p=0·005, *d*=0·71), episodic memory (p=0·036, *d*=0·54), attention and executive functions (p=0·039, *d*=0·48), overall cognitive performance (p=0·041, *d*=0·47), and the quality of life (p<0·001, *d*=0·99). Singing resulted in additional improvement in short-term memory and working memory (p=0·006, *d*=0·75), and improved caregiver wellbeing (p=0·026, *d*=0·85).[43]
Music therapy and music listening *vs* standard care[44]	1	98	Yes	Single	Behavioural and psychological symptoms of dementia	10 h in 10 weeks	No significant differences between the groups.
Music listening, singing, improvising, and talking *vs* standard care[45]	1	13	Yes	No	Neuropsychiatric symptoms, well-being, and carer–resident interaction	11 h in 22 weeks	Music group showed improvement in symptoms (p=0·002, *d*=2·32) and in levels of wellbeing (p<0·001, *d*=3·85). Staff in the intervention group reported enhanced caregiving techniques as a result of the programme.
Group music therapy *vs* standard care[46]	1	100	Yes	Single	Mood and cognition	6 h in 6 weeks	Group music therapy decreased depression (p=0·001, *d*=0·21) and delayed the deterioration of cognitive functions, especially recall (p=0·004, *d*=0·72). The effects were present 1 month after cessation of the intervention.
Music therapy (listening and singing) *vs* other activities[47–49]	3	76;[47] 77;[48] 59[49]	Yes	Single	Neuropsychiatric symptoms;[47] agitation;[48] behavioural and psychological symptoms[49]	21 h in 16 weeks;[47,48] 15 h in 16 weeks[49]	Neuropsychiatric symptoms decreased significantly in the music therapy group (p=0·01);[47] there were no significant differences between the groups;[48] music therapy improved behavioural symptoms (p<0·0001, *d*=1·04), functional ability (p<0·0001, *d*=0·79), and empathetic behaviour (p<0·0001, *d*=0·61) compared with the control treatment.[49]
Music therapy (listening, playing and singing) *vs* cooking[50]	1	37	··	Single	Patients' mood, cognition, behavioural disturbances, and stress experienced by their nurses	8 h in 4 weeks	There were no significant differences between the groups.
Music therapy *vs* standard care[51,52]	2	50;[51] 50[52]	Yes	Single	Cognition and anxiety;[51] behavioural disturbances[52]	18 h in 12 weeks;[51] 6 h in 4 weeks[52]	The music group improved performance in attention (p=0·001, *d*=0·76) and verbal episodic memory tasks (immediate p=0·001, *d*=0·76; delayed p=0·001, *d*=0·73), but not in anxiety;[51] music reduced the behavioural disturbances showed by significant group difference (p<0·05, *d*=0·63).[52]
Favourite music *vs* standard care[53]	1	52	No	No	Anxiety	6 h in 6 weeks	Anxiety decreased in the music group (p=0·004, *d*=0·06).
Music therapy (playing and listening) *vs* standard care[54]	1	100	Yes	No	Agitation	6 h in 6 weeks	There was no significant differences between the groups.
Music therapy (listening and playing) *vs* reading[55]	1	47	Yes	Single	Mood and quality of life	32 h in 16 weeks	There were no significant differences between the groups.
Music therapy *vs* resting and reading[56]	1	30	Yes	Single	Anxiety and mood	5 h in 16 weeks	Music therapy decreased anxiety (p<0·001, *d*=2·42) and depression (p=0·002, *d*=1·05). These effects persisted up to 2 months after stopping the intervention.

(Table continues on next page)

	Studies (n)	Partici-pants (n)	Music therapist involved	Blinding	Primary outcome	Overall duration of intervention	Main results
(Continued from previous page)							
Parkinson's disease							
Music listening, rhythmic clapping, or stomping *vs* standard care[57]	1	18	Yes	Single	Motor performance, cognition, and quality of life	12 h in 6 weeks	Music therapy improved mobility (p=0·006), UPDRS III (p=0·003), text recall (p=0·036), item naming (p=0·033), performance in Stroop test (p=0·007), and quality of life (p=0·031).
Favourite music synchronised to gait *vs* regular activities[58]	1	22	No	Single	Walking parameters	19·5 h in 13 weeks	Walking to music improved velocity (p=0·002, d=2·64), stride time (p=0·019, *d*=1·76), cadence (p=0·007, *d*=2·16), and UPDRS III (p=0·002, *d*=0·50).
Tango, waltz, or foxtrot dancing *vs* standard care[59]	1	48	No	Single	Functional motor control	20 h in 13 weeks	Tango group improved in balance (p=0·001, *d*=2·98), 6-min walking (p=0·001, *d*=2·50), and backward stride length (p=0·001, *d*=2·19); waltz or foxtrot group improved in balance (p=0·001, *d*=3·17), 6-min walking (p=0·001, *d*=2·24), and backward stride length (p=0·018, *d*=1·96).
Tango and waltz or foxtrot *vs* Tai Chi or standard care[60]	1	61	No	No	Health-related quality of life	20 h in 13 weeks	Tango improved mobility (p=0·03, *d*=2·50), social support (p=0·05, *d*=2·97), and quality of life (p<0·01, *d*=2·09).
Tango *vs* physical exercise[61]	1	19	No	Single	Functional mobility	20 h in 13 weeks	Tango group improved balance (p=0·01, *d*=2·18).
Multiple sclerosis							
Keyboard playing *vs* mute keyboard playing[62]	1	19	No	No	Hand function	7·5 h in 2 weeks	The music group improved in the functional use of the hand significantly more showed by time × group interaction (p=0·003, *d*=0·60).
RAS *vs* standard care[63]	1	10	Yes	No	Gait parameters	2 weeks	RAS significantly decreased double-support time (left: p=0·018, *d*=1·61; right: p=0·025, *d*=1·46).
Epilepsy							
Nightly exposure of Mozart Sonata K. 448 *vs* no intervention[64]	1	73	No	Single	Seizure occurrence	Every night for 1 year	Seizure frequency in the music group decreased significantly during the treatment phase (17%, p=0·014) and 1 year after treatment (16%, p=0·027).

Effect size (Cohen's *d*) was the mean change in outcome before and after treatment in the treatment group minus the mean pre–post change in the control group, divided by the pooled pre-test SD.[65] Effect size was defined as small (d≥0·2), medium (d≥0·5), and large (d≥0·8). *d*=Cohen's d. MST=music-supported therapy. RAS=rhythmic auditory stimulation. UPDRS III=Unified Parkinson's Disease Rating Scale part III.

Table: **Randomised controlled trials assessing various music-based interventions in patients with stroke, dementia, Parkinson's disease, multiple sclerosis, or epilepsy**

areas.[28] In addition to music listening, rhythmic auditory stimulation therapy improved patients' mood but the effect size was not significant.[36] Although positive effects were shown to last up to at least 6 months for some outcome measures, these results need to be replicated.

Music-based interventions for dementia

The most common causes of dementia are Alzheimer's disease, cerebrovascular diseases, or a combination of the two. In these disorders, neural degeneration can progress over several years, leading to memory problems and other behavioural disturbances. So far, 17 randomised controlled trials enrolling people with dementia (table) have assessed the effects of music-based interventions on neuropsychiatric and behavioural symptoms such as anxiety and agitation (14 studies),[40–42,44,45,47–54,56] depression (six studies),[42,43,46,50,55,56] cognitive status (five studies),[42,43,46,50,51] and quality of life (four studies).[42,43,45,55] Neuropsychiatric and behavioural symptoms were assessed with tests, rating scales, or questionnaires measuring overall symptom severity (eg, Neuropsychiatric Inventory, Cohen–Mansfield Agitation Inventory, Behavioural Pathology in Alzheimer's Disease rating scale), depression (eg, Cornell Scale for Depression in Dementia, Geriatric Depression Scale), cognitive status (eg, Mini-Mental State Examination [MMSE], Severe Impairment Battery), and quality of life or wellbeing (Cornell–Brown Scale for Quality of Life in Dementia, Dementia Care Mapping). Most interventions used vocal or instrumental music that was presumably familiar to the participants, such as personal favourites, general popular music, or common children's songs. In all studies except for one, the intervention was administered by a music therapist or music teacher.

Effects on cognitive deficits

In four studies, music listening coupled with cognitive elements (reminiscence and attention training) or physical exercise improved overall cognitive performance (measured by MMSE) of patients with dementia, compared with standard care (Cohen's *d*=0·47–0·76).[42,43,46,51] Additionally, improved performance in these music interventions was reported for tests measuring attention and executive functions (*d*=0·48–0·76),[43,51] orientation (*d*=0·71),[43] and verbal or episodic memory (*d*=0·54–0·76).[43,51] In one randomised controlled trial,[43] caregiver-implemented singing enhanced short-term and working memory (*d*=0·75), especially in participants with mild dementia. It also reduced caregiver burden (assessed with Zarit Burden Interview; *d*=0·85). By contrast, no significant changes in cognitive performance were observed for group-based music and

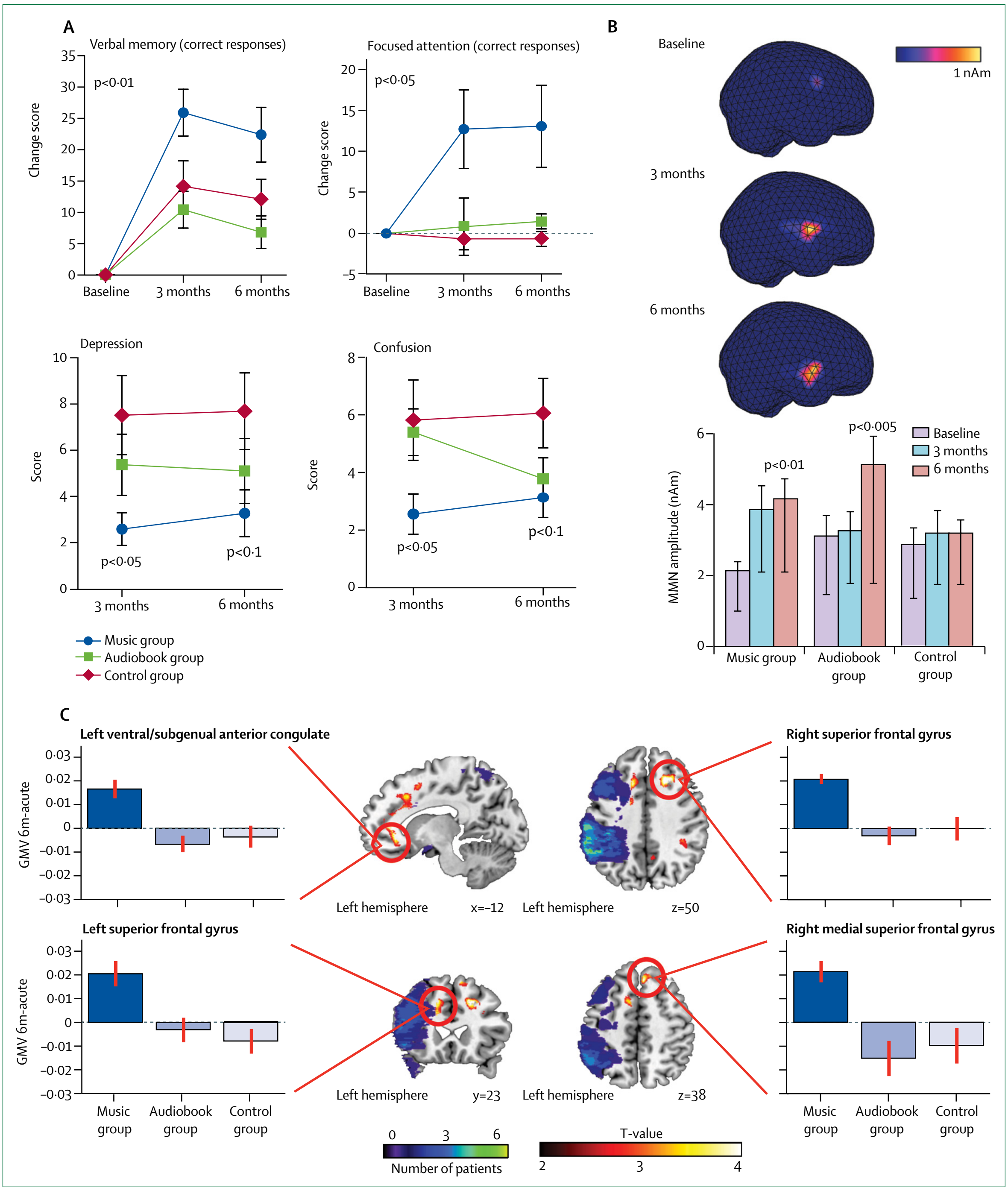

Figure 1: **Effects of daily music listening after stroke**

Cognitive, emotional, and neural effects of daily music listening (music group), audiobook listening (audiobook group), and standard care (control group) 1 week (BL), 3 months, and 6 months after stroke. (A) Neuropsychological results (mean and SEM) showing improved recovery of verbal memory and focused attention (baseline score subtracted from the values) and less depression and confusion in the music group compared with the audiobook and control groups. p values for verbal memory and focused attention calculated with mixed-model ANOVA. p values for depression and confusion calculated with one-way ANOVA. Adapted from Särkämö and colleagues.[33] (B) Magnetoencephalography group results (mean ± SEM) showing increased right hemisphere MMN responses to pitch changes in the music and audiobook groups compared with the control group. Adapted from Särkämö and colleagues.[32] (C) Voxel-based morphometry results of MRI data from patients with left-hemisphere damage (lesion areas in blue–green), showing larger GMV increases (mean ± SEM) in prefrontal and limbic areas in the music group compared with the audiobook and control groups. Results are shown at p<0·01 (uncorrected) with 50 voxels or more of spatial extent. T value shows GMV increases for the music group compared with the audiobook and control groups (Group × Time interaction). Adapted from Särkämö and colleagues.[28]
BL=baseline. nAm=nanoamperes. MMN=mismatch negativity. GMV=grey- matter volume.

cooking interventions in people with moderate-to-severe dementia.[50] The cognitive benefits of music observed only in the early stages of dementia might be related to enhanced cognitive reserve, the use of alternative networks, and cognitive strategies to cope with advancing pathology.[70]

Effects on neuropsychiatric symptoms, mood, and quality of life

Results from six studies showed that music therapy was efficacious in improving the neuropsychiatric symptoms of people with dementia (Cohen's d=0·42–2·32).[41,42,45,47,49,52] Three of these studies assessed the duration of effect after cessation of the intervention,[41,46,56] which varied from less than 4 weeks to 2 months. In one of the six studies, the music intervention programme also resulted in improved participant–caregiver interaction, measured by semi-structured interview, and improved participant wellbeing (d=3·85).[45] By contrast, two studies did not show any significant effect of music therapy or music listening on neuropsychiatric symptoms.[44,50] Regarding specific neuropsychiatric symptoms, results from two studies showed that music reduced anxiety and agitation in people with dementia,[53,56] but the effect sizes diverged (d=0·06 *vs* d=2·42). By contrast, results from four randomised controlled trials showed music to be ineffective in reducing anxiety or agitation.[40,48,51,54]

Quality of life was assessed in three studies.[42,43,55] Although Cooke and colleagues[55] did not find any significant differences between the effects of music and the control intervention (interactive reading), Särkämö and colleagues[43] reported that music listening compared with standard care substantially increased quality of life (Cohen's d=0·99),[43] especially in people with moderate dementia with causes other than Alzheimer's disease.[42] Decreased depression or improvement of mood in people with dementia has been reported in four studies (d=0·21–1·05).[42,43,46,56] Two other randomised controlled trials did not show such an effect.[50,55] In both of these studies, the control group received an intervention other than standard care, raising the possibility that any pleasurable activity improved mood. Overall, the effects of musical interventions in dementia could be driven by the comfort and emotional safety induced by familiar music, which can temporarily overcome confusion and disorientation by anchoring a person's attention on a positive familiar stimulus in an otherwise confusing environment. We speculate that this anchoring effect could be enhanced by using headphones. Familiar music can also be imbued with emotions that are specific to an individual, and can trigger autobiographical memories and help to temporarily restore a sense of identity.

Music-based interventions for Parkinson's disease

Patients in the early stage of Parkinson's disease can have deficits of the autonomic nervous system and other non-motor deficits, and 30% of patients develop dementia-level cognitive decline in the late stage of the disease.[71] The effect of music on several symptoms of Parkinson's disease have been studied in five randomised controlled trials (table).[57–61] Four studies examined the effects of music-assisted motor training using motor parameters as outcome measures.[57–59,61] Two studies[57,60] evaluated non-motor parameters, quality of life, cognition, or social parameters. In all studies, medication for Parkinson's disease remained unchanged during the interventions.

General motor performance was assessed using the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS-III), and specific motor functions using, for example, the Berg Balance Scale and 6-min walk test. Specific gait parameters were analysed using video recordings and computer-assisted motion analysis programs. Quality of life was evaluated using validated questionnaires. Music used in the intervention varied from rhythmic auditory cueing to self-selected favourite music, although the genres of the patient's favourite music were not reported. A music therapist administered the intervention in only one study.[57]

Based on effect sizes we calculated from the published data, dancing had the most consistent and clinically significant beneficial effect on motor symptoms. In one study of 48 participants,[59] both tango and waltz or foxtrot intervention groups improved in balance (Cohen's d=2·98 for tango, d=3·17 for waltz or foxtrot), 6-min walk test (d=2·50, d=2·24), and backward stride length (d=2·19, d=1·96) compared with standard care.[59] In a smaller study of 19 participants,[61] tango improved balance (d=2·18). Dancing also improved overall mobility in another study (d=2·50).[60] Music therapy with rhythmic movements—which uses a coupling of movement and music that is similar to dancing—improved overall mobility in patients with Parkinson's disease.[57] In another study,[58] gait training synchronised to music resulted in improved velocity (d=2·64), stride time (d=1·76), and cadence (d=2·16).[58] Both studies reported a reduction in Parkinson's disease-specific motor symptoms (d=0·50).[57,58]

Results from two studies[57,60] showed that a music-based intervention improved quality of life, with large effect size. Dancing the tango appeared to be significantly more effective than waltz or foxtrot, tai chi, or regular treatment (d=2·09).[60] Additionally, patients reported better social support after the intervention (d=2·97). Improvements in cognition were reported in one study.[57]

Although the sample sizes in these studies were relatively small, the evidence suggests that dancing and music-based interventions that synchronise movement to music can be beneficial in the maintenance of motor performance in people with Parkinson's disease. Rhythmical use of musical stimuli compensates for the loss of control by the extrapyramidal system and enhances audio perception and movement synchronisation.[30,37,38] The perceived rhythm in music activates the neural

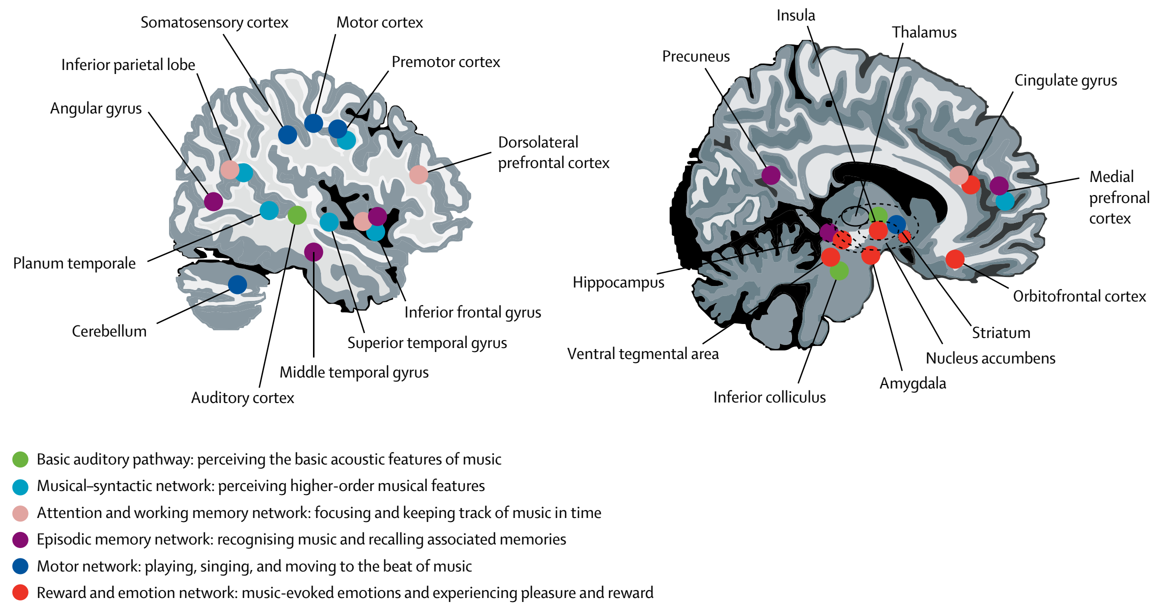

***Figure 2*: Key brain areas associated with music processing**
Areas identified from neuroimaging studies of healthy people. Although the figure displays the lateral and medial parts of the right hemisphere, many musical processes are largely bilateral (with the exception of pitch and melody processing, which are lateralised, the activity in the right hemisphere being dominant). Adapted from Särkämö and colleagues.[16]

circuits involved in motor actions and acts as an external cue for movement, thus replacing the impaired internal timing function in people with Parkinson's disease.[72] As in studies of stroke rehabilitation,[22] the use of music as a stimulus might be more effective than auditory stimulation without music (eg, metronome beat) in gait rehabilitation, but requires further investigation. Similarly, external cueing might also explain the positive effects of dancing in people with Parkinson's disease. Furthermore, the improvement in motor control and possible decrease in disease-specific symptoms might in turn improve quality of life. In all reviewed studies, the follow-up period was too short to draw conclusions on the long-term effects of music interventions. The effects of music on the autonomic disturbances in Parkinson's disease have not been addressed in controlled studies.

Music-based interventions for multiple sclerosis

Multiple sclerosis is one of the most common neurological diseases in the young adult population, with disease onset occurring in most cases between the ages of 20 and 40 years. Despite relatively low prevalence, patients with the disease require expensive medication and in most cases life-long rehabilitation.[3] Multiple sclerosis treatments aim to ameliorate function after flare-up of an episode or to prevent new episodes. Only two randomised controlled trials[62,63] have studied the effect of musical interventions in alleviating the manifestations of multiple sclerosis (table). Between these studies, outcomes were different, and the intervention was administered by a music therapist in only one study.

The trial without a music therapist[62] included 19 patients and studied the effect of keyboard playing (audible *vs* mute) in hand functionality. Audible keyboard playing significantly improved the functional use of the hand (Cohen's $d=0\cdot60$), as indicated by a validated questionnaire (ABILHAND). Using a computerised gait analysis, a feasibility study[63] of ten patients with multiple sclerosis and gait problems found rhythmic auditory stimulation to be effective in decreasing double-support time ($d=1\cdot46–1\cdot61$).[63] Although decreased double-support time might reflect improved dynamic balance,[73] none of the other gait parameters tested in this study differed from controls receiving standard care. The results of music-based interventions in multiple sclerosis are scant and allow no definite conclusions on the rehabilitative effect of music. Although designing studies can be challenging because of the diversity of disease deficits, motor functions, spasticity, fatigue, cognitive deficits, and mood might be feasible outcome measures in the future studies.

Music-based interventions for epilepsy

Epileptic seizures arise from abnormal synchronisation of electrical activity in the brain, and most of them cease spontaneously, by largely unknown mechanisms. Exposure to patterned auditory stimuli provides a non-invasive excitatory stimulation of the cortex, which might reduce epileptiform activity.[74] To test this hypothesis, one randomised controlled trial (table) examined the efficacy of music in patients with epilepsy.[64] Patients were exposed to Mozart's music at periodic intervals every night for

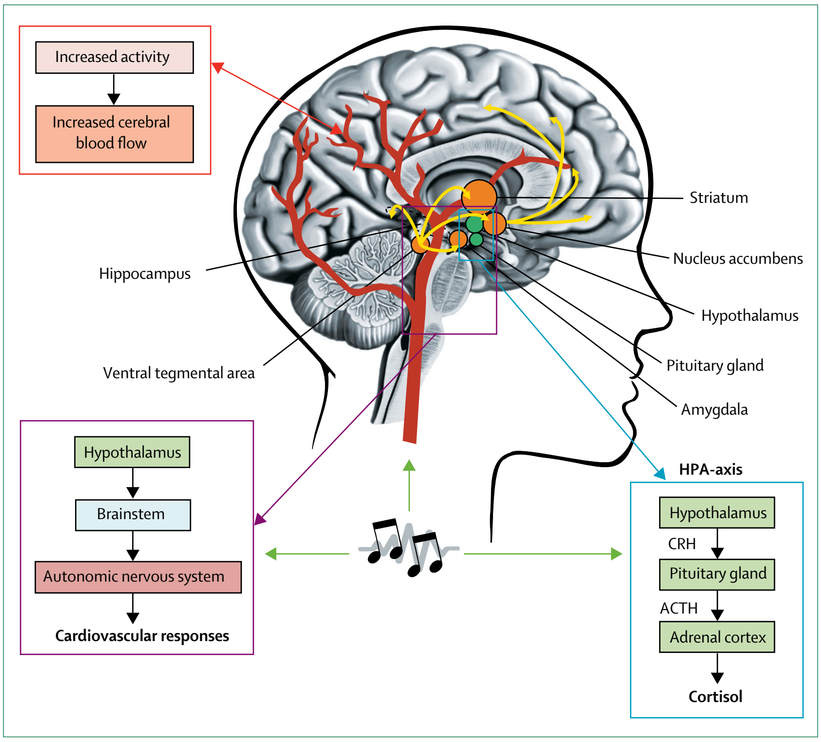

Figure 3: **Possible neurobiological mechanisms for the rehabilitative effect of music**
Orange circles and yellow arrows represent the mesolimbic system, and the green circles represent the HPA axis. ACTH=adrenocorticotropic hormone. CRH=corticotropin-releasing hormone. HPA axis=hypothalamic-pituitary-adrenal axis.

1 year, and a significant 17% reduction in seizure frequency was detected during the study period (p=0·014). Additionally, a carry-over effect of 16% reduced seizure frequency persisted for 1 year. Although no other randomised controlled trials with adult participants have been published, a recent meta-analysis of 12 studies including both children and adult patients with epilepsy of any kind indicated that 130 (85%) of 153 patients responded favourably to music, with an average reduction in interictal epileptic activity of 31% during the listening period and 24% after the listening period.[75] Further studies are needed, since only two of these studies had a separate control group.

Mechanisms underlying the rehabilitative effect of music

Considering the widely varying nature of the diseases in which music has led to improved recovery, enhanced rehabilitation, or alleviation of symptoms, several distinct explanatory mechanisms can be postulated.

Neural activation and neuroplasticity

Results from functional neuroimaging studies in healthy participants have shown that music induces widespread activation of various networks in the brain[14–17] (figure 2), and correspondingly increases blood flow through the medial cerebral artery because of autoregulation[76] (figure 3), which should provide favourable circumstances for recovery in general. For example, after stroke, neuroplastic changes associated with functional recovery are activity-dependent.[77] Musical activities bear similarity with the concept of enriched environments used in animal studies, which facilitates recovery at behavioural and neurobiological levels in animal models of many neurological illnesses.[13]

Since active music-based rehabilitation involves multiple components analogous to training and music learning (ie, iterated practice of movements coupled with auditory feedback and extensive cognitive processing), it is plausible that music-based neurological rehabilitation induces similar structural and functional neuroplastic changes seen in populations of healthy individuals that receive musical training.[18,19] Indeed, some studies have reported memory-related plastic effects after music listening,[28,32] as well as neural reorganisation after music-supported therapy in patients recovering after a stroke.[34] Other studies have provided further evidence of auditory-related and motor-related neuroplasticity after music-supported therapy[78–80] and melodic intonation therapy[81] in patients who have had a stroke.

However, the specific cellular mechanisms of music-induced neuroplasticity remain unknown. Although substantial neurogenesis in elderly individuals seems unlikely, other putative mechanisms include neuronal hypertrophy, increased volume of neuropil, and changes in the vascular or glial compartments. An intriguing question to investigate would be whether previous music exposure during a specific period of lifetime affects the plasticity of the recovering brain. The possibility of negative plastic changes due to overly intense or premature intervention should be considered.

Activation of reward, arousal, and emotion networks

Music activates the dopaminergic mesolimbic system, which regulates memory, attention, executive functions, mood, and motivation[82] (figure 3). A key part of this reward system is the nucleus accumbens, which regulates mood and pleasure. In healthy individuals, its activation by an intense emotional response to music (so-called chills) leads to increased dopamine secretion directly proportional to the intensity of the experience.[82] Increased extracellular dopamine levels could partly explain the cognitive–emotional gains induced by music in patients with neurological disorders. Music-induced improvement of mood, arousal, and relief of confusion might therefore enhance recovery of cognitive functions in these patients. Music-induced activation of the parasympathetic nervous system and inhibition of the sympathetic nervous system in people with dementia, and corresponding changes in catecholamine and cytokine secretion, has been considered as a soothing effect of music.[83] This increased parasympathetic activity is also a possible mechanism behind the effect of music ameliorating neuropsychiatric symptoms in dementia.

Music also produces measurable cardiovascular and endocrine responses, indicated by reduced serum cortisol levels and inhibition of cardiovascular stress reactions[83,84] (figure 3). In animal models, prolonged stress can have maladaptive effects on neuroplasticity, such as dendritic atrophy, synapse loss, and decreased hippocampal neurogenesis.[85] Elevated cortisol levels in patients with acute stroke correlates with increased infarct volume, and increases the risk of depression, poor prognosis, and fatal outcome.[86] We speculate that listening to music might lower stress hormone secretion in acute stroke, as it does in postoperative patients.[87,88]

Overall, neurological diseases and mood disorders have a high comorbidity, ranging from 20% to 50%.[89,90] Common clinical experience is that depression diminishes adherence to rehabilitation, and studies indicate that depression impairs functional outcome and quality of life, and increases mortality.[91] According to the data discussed previously, music improved mood or diminished anxiety in people with dementia[43,53] and in patients who have had a stroke.[33,36] We conclude that music interventions are viable in improving the mood of patients with neurological disorders. However, the causal relationship between music-induced mood improvement and neurological outcome remains to be proved.

Activation of alternative or spared neural networks

Some music interventions engage specific regions associated with musical rhythm, movement, singing, or memory that are not directly affected by the disease.[72] Rhythmic entrainment, our inherent tendency to time movements to the regular beat of music, which forms the basis of rhythmic auditory stimulation and playing-based music interventions, is based on the strong connectivity between the auditory system and motor system.[14] In diseases in which the internal sequencing and monitoring of actions does not work because of motor system dysfunction, rhythmic entrainment can act as an external timer, cueing the execution of movements, and therefore bypassing the dysfunction.[72] For instance, a patient with impaired muscle coordination after a stroke, or a patient with Parkinson's disease with stiffness and bradykinesia, might find it easier to execute motor tasks with rhythmic support provided by music listening or dancing.[30,37–39,57–59,61]

Singing, which is the key component of melodic intonation therapy, engages frontotemporal language and vocal-motor regions bilaterally, and more extensively, than does speaking.[92,93] This engagement enables training of speech in patients with aphasia via both spared left hemisphere regions and homologous right hemisphere regions. The preserved ability to sing in patients with aphasia has been reported as early as in 1745, when a patient with severe aphasia after a stroke was reported to be only able to verbalise the word yes, but was able to correctly sing familiar hymns, producing both the melody and the text of the songs.[94]

Familiar music specifically activates the anterior cingulate and medial prefrontal cortex in the healthy brain, suggesting that these regions are important in musical memory.[95] In people with Alzheimer's disease, the medial prefrontal cortex degenerates more slowly than do other cortical regions, and the regions that encode musical memory also show minimal atrophy or decrease in glucose metabolism, despite amyloid-β deposition.[95] These observations provide a potential explanation for why patients with Alzheimer's disease are able to recognise and respond emotionally to familiar songs, even at late stages of the disease.[95]

Conclusions and future directions

Long-term treatment and rehabilitation for patients with neurological diseases accounts for a substantial proportion of the associated costs, and therefore, study of novel rehabilitation strategies to replace or complement traditional methods is warranted. With this aim, the effects of music-based rehabilitation in major neurological disorders have been studied in 41 randomised controlled trials to date. Music interventions seem to be beneficial, particularly in motor rehabilitation for people with stroke and Parkinson's disease. Additionally, music interventions can have favourable effects on cognition, mood, and quality of life in people with stroke or dementia.

Although the majority of studies have reported positive effects, the possibility of publication bias should be considered. In addition, only a few of the primary outcomes have been studied repeatedly. Limitations in most studies arise from small sample sizes and methodological heterogeneity in study design, and in the interventions and outcome measures used. In most studies, the duration of the music-induced rehabilitation effect was not systematically evaluated and is still largely unknown. Thus far, music-based interventions have been observed to have long-term effects in stroke (3 months),[33] dementia (maximum 2 months),[41,46,56] and epilepsy (12 months).[64]

In some studies, the difference between active and receptive intervention and the role of the music therapist (if participating) remained unclear. The therapeutic relationship between patient and therapist that is inherent in formal music therapy is likely to have an additional effect on the outcome. Although this aspect is difficult to delineate from the music intervention used, the outcome of an intervention given by a music therapist might in some cases be superior to that given by another health-care professional, as has been observed for rhythmic auditory stimulation in gait rehabilitation.[22] However, the studies reviewed here showed that both music therapy and other music-based interventions have beneficial effects regardless of the involvement of a dedicated music therapist. Most of the studies did not have an adequate description of the music type used. Since music types can greatly vary (eg, stimulating *vs* soothing), their expected effects on physiological parameters, arousal, and affect regulation differ. Furthermore, most of the reviewed studies did not use patient-selected or favourite music. Because of the strong emotional components of musical experience, using patient-selected music could be beneficial since it can be considered more meaningful and rewarding to the patient than generic music.

Additional high-quality intervention studies, particularly large-scale trials such as cluster-randomised, multicentre randomised controlled trials, in which the established music interventions are embedded into the clinical rehabilitation practice, would be needed to establish the efficacy and feasibility in real-life settings of these approaches. For better comparability of the studies, it would also be important to use common outcome measures, clearly document the type of the intervention (active *vs* receptive) and music used (patient-selected *vs* experimenter-selected), as well as define the optimal time of onset and legnth of the music interventions, and determine the long-term duration, if any, of their rehabilitation effects. In addition, multimodal studies combining behavioural outcome measures with neuro-imaging and neuroendocrinological markers are needed to determine specific neurophysiological mechanisms and effects of various music-based interventions in patients with a neurological disorder.

Analysis of the amount of core therapeutic activities received by patients in one rehabilitation centre in Canada, such as physiotherapy and occupational therapy, suggests that patients who have had a stroke receive only approximately 60% of the recommended rehabilitation.[96] It is unclear whether this insufficiency results from scarceness of rehabilitation resources or other factors, but is likely to be generalisable to most neurological wards. Thus, there is a need for music interventions that are widely available and can easily be implemented with minimal investment. These interventions include self-implemented or caregiver-implemented musical activities, such as music listening, and group-based musical interventions, such as group singing or dancing.

In the future, mobile music applications (eg, music streaming, games), as well as novel music-based rehabilitation technology using virtual reality or adaptive music stimulation systems tailored for motor rehabilitation, will play an increasing role in bringing music to patients with neurological disorders, in hospital, community, and home environments.

Search strategy and selection criteria

We searched PubMed for papers published in English before April 11, 2017, using the Medical Subject Headings "stroke", "brain injuries", "dementia", "parkinsonian disorders", "epilepsy", and "multiple sclerosis", combined with "music" or "music therapy" and the keywords "melodic intonation therapy", "rhythmic auditory stimulation", "rhythmic auditory cueing", and "music supported therapy". Additional references were gathered from reference lists and relevant articles. We included only the randomised controlled trials that applied at least a 1-week intervention, and we focused on scientific literature of the past 10 years, but we also included two older landmark studies.

Contributors

AJS, VL, and SS searched and reviewed the literature. AJS created the figures and the table, and AJS and SS wrote the primary manuscript, which was circulated among the other authors (TS, EA, MT, and VL). All authors made substantial additions on the basis of their special areas of interest, which were incorporated into the final manuscript.

Declaration of interests

We declare no competing interests.

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