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WHY IS IT THAT RESEARCH INTO THE EFFECTS OF MUSIC ON DEMENTIA WITH LEWY BODIES IS SO URGENTLY NEEDED?

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Abstract

This review argues why research into the effects of music on Dementia with Lewy Bodies (DLB) is urgently needed. In this sense, in inquiring into the possibility of using music therapy as a psychosocial intervention in the management of DLB, it begins with a brief presentation of human aging, followed by the presentation of DLB and of how DLB fits into human aging, followed by the presentation of the effects of physical activity and the reasons why it cannot be used as a viable psychosocial intervention in the management of DLB. Finally, this review presents the evidence on the effects of music on dementia and the reasons and arguments why research into the effects of music on DLB is so urgently needed. Live music seems to be significantly associated to a short-term lessening of apathy in dementia.

Keywords: music therapy, dementia with Lewy bodies, physical activity, human aging

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On the intended goals of this review

The aim of this review is to argue why research into the effects of music on Dementia with Lewy Bodies (DLB) is so urgently needed. In this sense this review inquires into the possibility of using music therapy as a psychosocial intervention, in alternative to physical activity, in the management of DLB, considering that the clinical practice shows that elderly people suffering from DLB are not willing to dedicate themselves to their bodies. This review will then begin with a brief presentation of human aging, followed by the presentation of DLB, the very syndrome that killed Immanuel Kant (Miranda, Slachevsky, & Garcia-Borreguerro, 2010), and then it will explain how DLB fits into human aging. After that, the effects of physical activity will be presented and it will be argued the reasons why it cannot be used as a viable psychosocial intervention in the management of DLB. Finally, this review will present the evidence available on the effects of music on dementia and conclude why research into the effects of music on DLB is so urgently needed.

Immanuel Kant (1724-1804)

Psychosocial interventions are nonpharmacologic interventions that have the potential to improve many of the symptoms and functional impairments associated with DLB. It is already well-known that behavioural and psychiatric or psychological symptoms of dementia (BPSD) and also cognitive symptoms of dementia can be worsened by low levels of rousing and attention and that psychosocial interventions that furnish environmental novelty may reduce these symptoms and their impact.

On human aging

Despite the huge increase in the number of very old people, even supercentenarians, the human possibility of growing old does not seem to be an evolutionary recent event. Greve and Bjorklund (2009) argue that the recent human longevity is related to the accumulated experiences and knowledge and wisdom that older members of human groups were providing along human evolution. The experience of older people and their contribution to the fulfilment of a need or furtherance of an effort or purpose to their own relatives and to closest members of the group, along human evolution, probably became targets to natural selection. Such an enhancing effect of the possibility of contribution from some older members of a group is called "Nestor Effect", that is, the effect of the integrated and accumulated knowledge of some older members of the group. Greve and Bjorklund (2009) devised the term "Nestor Effect" inspired by Homer's Iliad that describes heroic legends during the wars between the Greeks and the Trojans and where the King Nestor, wise ancient around 110 years of age, famous for his courage and smooth-spoken, frequently gave advice to younger warriors, inspired the troops and drove his war vehicle.

The argument for the "Nestor Effect" is that the oldest people, and consequently the human possibility of becoming old, truly represents an advantage, a benefit, not only to older people themselves but also to their offspring, relatives and immediate neighbours. Growing old, despite the loses, may be interpreted as an evolutionary adaptation. Available evidence shows that while information processing velocity and working memory capacity may decrease with aging, accumulated experience and knowledge do not present a negative tendency, what gives support to the argument that these memories, the accumulation of the results from experiences with differing environmental contingencies, are the most valuable capital of older people. The oldest memories, that is, the elderly's memories, are probably the memories that make Nestor's memories unique and incomparable. The presence around of some old people that possess information that can be necessary from time to time and that can integrate their accumulated experiences would certainly provide an adaptive advantage to the members of the group.

The availability of many wise ancients could be interpreted as a preadaptation for eusociality where the oldest members of the group would contribute to the satisfaction of the needs of the youngest ones and provide impetus for their efforts and purpose and that, in turn,

would increase adaptation for those who took care of their oldest. Eusociality is a life course strategy observed in animals that live in complex societies. In such societies, for instance among bees and ants, a subgroup of members of a group reproduce themselves while other members of the group function as nonreproductive caretakers. Species truly eusocial present three characteristics: generational superposition, division of labour and cooperative care of the youngest (Colman, 2006). The benefit of the presence of the oldest members depends however on the number of older people available and the quality of their cognitive functioning (for instance, prevalence of dementia).

It is true that during aging, while many individuals experiment decline in certain cognitive abilities, many individuals age in a healthy manner and can sustain high levels of cognitive functioning during their lifetime (e.g., Dunnen et al., 2008). Aging does not seem to be synonym with cognitive incapacity. Even the decline experimented by many individuals usually is not malignant but occurs in parallel to certain declines in physiological functioning that, in turn, occurs in conjunction with normal developmental processes. Each individual has an elaborated and mainly unknown history what confers a certain individuality, that is, different individuals age in different ways (e.g., Antonini et al., 2008). For some individuals, however, the changes in certain cognitive abilities go beyond what could be considered normal and present themselves as persistently progressive. Such forms of malignant cognitive decline are caused by a variety of neuropathological conditions, among them DLB (10%-15% of all cases of dementia) and Parkinson's Disease Dementia (PDD) (e.g., Bertelli, Raposo, & Fernandes, 2007; Bertelli, Bianchi, & Cruz, 2009; Bertelli, Bianchi, & Cruz, 2010).

On DLB

Despite all differences, neurodegenerative diseases have in common the abnormal accumulation of certain proteins and, because neurons are particularly vulnerable to the toxic effects of these changes in the structure of the proteins, chronic and silent inflammatory processes may be triggered (e.g., Bertelli, Raposo, Bianchi, Fernandes, & Cruz, in press).

DLB is the second most common cause of neurodegenerative dementia in elderly people and, due to the hallucinations presented in the early stages of the disease, antipsychotic drugs are prescribed which has secondary effects that are extremely noxious to the

extrapyramidal system. The primary function of the extrapyramidal system is the fine tuning of the voluntary movements in the sense of making them malleable to the higher levels of conscientious control. The absence of such a fine tuning endangers voluntary movements, for instance, by the presence of tremors, spontaneous movements, rigidity, slower motor movements, and spontaneous characteristics of Parkinson's Disease (PD), in other words, extrapyramidal symptoms (EPS). Even in low dosage, people with DLB that do not present changes in the extrapyramidal motor system are extremely susceptible of developing such alterations when medicated with antipsychotics (e.g., Bertelli et al., 2009; McKeith, 2006).

DLB is part of a spectrum called Lewy bodies disease. Such spectrum contains neurodegenerative diseases that share the unbalance and abnormal accumulation of a synaptic protein called alpha-synuclein (e.g., Spillantini et al., 1997). Clinical manifestations of the spectrum include DLB and PDD. Such manifestations share some pathological changes such as the formation of Lewy bodies, that are microscopic protein deposits in the brain. Fritz (or Friederich or Frederick) Heinrich Lewy discovered, in the brains of individuals with PD, an infinitesimal substance that later became known as Lewy bodies. The term Lewy bodies was included in the international literature in 1918 (Schiller, 2000).

Friederich Heinrich Lewy
(19885-1950)

Proteins are substances that have the function of liberating energy and repairing tissue and cell. The protein alpha-synuclein, in particular, usually protects the cells from damage but its accumulation leads to the formation of Lewy bodies. DLB central characteristics, that is, serving as an essential component for the diagnosis of possible or

probable DLB are: dementia defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function, and deficits of attention, executive function and visuospatial ability. Memory impairment may NOT necessarily occur in the early stages. Deficits of attention create difficulties in the capacity of cognitive inhibition, that is, the capacity to limit the quantity of information in the working memory and resolve potential interferences during processing. Interference and inhibition seem to contribute to a large spectrum of BPSD and cognitive symptoms (e.g., Bertelli, Costa, & Bianchi, 2009). Elderly people with DLB seem to be particularly impaired in their capacity of cognitive inhibition, even when compared to those diagnosed with dementia of Alzheimer (Costa, 2011).

DLB core clinical characteristics, that is, the ones most prime or most essential or most vital, for the diagnosis of a probable or possible DLB, are the cognitive fluctuation with repeated visual hallucination and EPS. The specificity of a clinical diagnosis of probable DLB, defined by the presence of two or more of these most prime characteristics, represents the criteria in more than 80% of the cases, however, according to McKeith (2007), in around 50% of the cases the identification is made using only these criteria. In clinical practice, in order to improve the rate of case identification, a higher index of suspicion is adopted considering the criteria of the presence of only one of the most prime characteristics in the clinical diagnosis of possible DLB. Thus, the consensus guidelines for the clinical and pathologic diagnosis of probable and possible DLB (e.g., McKeith, 2006) specifies a set of the most prime clinical characteristics (two of them essential for the diagnosis of probable DLB and one essential for the diagnosis of possible DLB): irregular cognition with pronounced attention variations and readiness to respond, persistent visual hallucinations, and EPS.

There are also three additional suggestive (that imply or connote) characteristics of DLB, that is, characteristics that present themselves as significantly more frequent than in other forms of dementia and that occurring in isolation or in combination in a individual presenting progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function, give support for the diagnosis of DLB: Rapid Eye Movement (REM) sleep behaviour disorder, extreme sensitivity to the side effects of antipsychotics, and low dopamine transporter uptake by the basal ganglia according to Single Photon Emission

Computed Tomography (SPECT) or Positron Emission Tomography (PET) (e.g., Boeve, Silber, & Ferman, 2004). Basal ganglia disturbances produce characteristic motor, cognitive and emotional symptoms.

If the characteristics mentioned above are present together with one or more of the core/most prime/most essential clinical characteristics it is enough for a diagnosis of probable DLB (Table 1). There are some auxiliary characteristics, that is, characteristics that furnish added support, characteristics that may be present but that do not constitute the most important elements, characteristics which commonly occur but with lower specificity: repeated falls, faints, brief loses of consciousness, delusions, hallucinations in domains other than visual (for instance, auditory hallucinations) and apathy.

The temporal sequence of events is extremely important considering that it is already well-known that when the person presents only EPS, the problem will be PD, but when EPS are followed (within 12 months) by cognitive symptoms, the problem will be DLB, however, when EPS are followed (after more than 12 months) by cognitive symptoms, the problem will be PDD, which tends to manifest itself in the later phases of PD (e.g., McKeith, 2006). Usually, the onset of DLB tends to be inconspicuous, very difficult to detect, and the elderly themselves and their closest relatives do not realize that something very wrong is going on inside the person, but such onset is very destructive. The presence of a period of increasing confusion, the identification of the presence of hallucinations or a major fall may give the wrong impression of a sudden onset, however the unfold of DLB is progressive.

Investigations through neuroimaging resources may give some support to the clinical diagnosis. The neuropsychological profile of the damages in DLB reflects the combined involvement of cortical and subcortical pathways and a relative preservation of the hippocampus. Elderly people diagnosed with DLB present poor performance in visuospatial and attention tasks (e.g., Sauer et al., 2006). Fluctuation in cognitive functioning, that becomes altered in minutes, hours or days, occur in 50%-75% of the cases and are associated with the continuous variations in the levels of attention and readiness to respond. Closest relatives have the opportunity to observe the presence of daytime somnolence, episodes when the individual stares without any expression to nothing and also an incoherent speech.

Visual hallucination is the most characteristic BPSD in DLB and its persistence helps in differential diagnosis. Visual hallucinations are present in half the cases of DLB at the onset

and occur sometime during the course of the disease in the majority of the cases. Such hallucinations, typically well formed and detailed, provoke varied emotional responses.

Table 1. Indicators for the diagnosis of Dementia with Lewy Bodies (DLB)

1) Presence of at least one of the most prime/most essential/core characteristics:
a) visual hallucinations, cognitive fluctuation OR b) spontaneous characteristics of Parkinson's Disease
OR
2) One of the suggestive characteristics:
a) REM sleep behaviour disorder, severe sensibility to antipsychotics OR b) low dopamine transporter uptake by the basal ganglia
AND
3) Attention deficits, sleepiness during the day and apathy
4) Relative preservation of episodic memory
5) Significative visuospatial and executive impairment
6) Urinary incontinence, dizziness and falls
7) Absence of atrophy in the medial temporal lobe according to: computerized tomography / magnetic resonance
8) Good response to cholinesterase inhibitors

The profile of EPS in DLB is generally similar to the profile of EPS in DP however with greater postural instability, facial apathy, and less tremor. An abnormal sensitivity to the side effects of antipsychotics, as previously mentioned, occurs in 50%-60% of DLB cases when traditional antipsychotic agents are prescribed and such a severe sensibility is associated to a significant increase in mortality risk due to the intense beginning or worsening of EPS and consciousness impairment. Atypical antipsychotics, if prescribed in small dosage, can be safer but sensibility reactions have been documented for the majority of this agents (e.g., McKeith et al., 2004).

Some characteristics of DLB are also present in narcolepsy, that is, a sleep disorder characterized by sudden and uncontrollable episodes of deep sleep (REM sleep behaviour disorder, daytime very sleepy state, visual hallucinations and loss of muscular tone in response to emotional stimulation). REM sleep is that timing of deep sleep that occurs some time after the individual falls asleep, when the eyes begin to move under the eyelids (e.g., Boeve et al., 2004).

Symptoms of depression (disinterest in every or almost every sort of activity during all day long and almost every day, loss of weight in the absence of diet, increase or decrease of appetite almost every day, sleep disorders, lack of energy almost every day, feelings of inferiority or guilt, diminished ability of concentration) are present in 33%-50% of DLB cases (e.g., McKeith, 2007).

On how DLB fits into human aging

In the five million years of the great apes evolution, prehuman primates evolved to today's Homo Sapiens Sapiens. In order to survive, prehumans had to abandon their lives in trees and consequently they had to modify their habits. The acquisition of bipedal locomotion brought huge changes in their locomotor apparatus and in their brain. Such changes resulted in an increase in brain volume due to the development of new cortical areas and brain pathways. Such improvements allowed for the development of, for instance, fine motor coordination, new cognitive functions, working memory, visuospatial perception, and high level of white matter. These still evolving new brain areas and cortical pathways are living longer than ever before, contributing, or having the effect of making happen, or becoming more likely the development of sporadic neurodegenerative diseases associated to aging. In a very stimulating, interesting and energising discussion, Ghika (2008) explains what happens to the brain in age-related neurodegenerative diseases. Systems that degenerate translate disturbances in these most recent cerebral areas that are specific to human primates, because neurodegeneration occurs in exactly those neural pathways phylogenetically most recently developed. DLB represents one of these sporadic age-associated manifestations of premature aging of newly developed cerebral areas, in this case, the extrapyramidal system (fine tuning of voluntary movements).

Human longevity or the potential to become old has always been a possibility along

the evolution. As previously mentioned, aging was pinpointed as a favourable characteristic and as such it became more common along successive generations of human primates. In other words, aging has evolutionary advantages. Adding to such adaptive value, during the last centuries, average life expectance grew in an astonishingly, in an amazing manner, to everyone's surprise due, probably, to the fast improvement in health services, medical technology, nutrition, hygiene, and a reduced rate of mortality. Such social improvements allowed for the unstable survival of human primate's new and still evolving brain areas and cortical pathways, creating conditions for the sporadic development of neurodegenerative diseases. In other words, the phylogenetically most recent brain areas and pathways seem to be still specifically sensitive, susceptible to the biological consequences of normal aging, such as decreasing number of dopamine receptors, diminishing volume of various brain structures, diminishing density of axon bundles, and diminishing velocity of the information processing system (IPS) (Park & Reuter-Lorenz, 2009).

On the effects of physical activity

Considering the increasing number of old and very old people, the proliferation of age-associated neurodegenerative diseases and the potential benefit of the presence of healthy elderly individuals in society, studies in the area of psychoneuroimmunology are continuously providing epidemiological evidence associating psychosocial variables, such as physical activity, to low rates of morbidity and mortality and also associating the quality, intensity and frequency of physical activity to the body inflammatory responses. Physical activity alone seems to lower the level of production of pro-inflammatory cytosine and, if practiced regularly, it diminishes inflammation and influences the production of anti-inflammatory cytosine. There is a considerable amount of evidence that physical activity is profoundly beneficial to cognitive functioning, improving codification, consolidation, storage, recollection and working memory, that are essential for human learning and memory. Because physical activity increases cardiovascular and aerobic capacities and, in particular, the brain's blood flow, it diminishes chronic inflammation in the nervous system and increases neuroplasticity (Bertelli et al., in press).

Many differing studies suggest that a particular factor that contributes to the positive effects of physical activity on EPS is the intensity of physical exercises, that is, most vigorous

activities improve motor functioning and regulation of dopamine. More demanding, forced exercises, that is, interventions in which the individual is forced to keep, for instance, a velocity above the preferred one, improves motor function and provides neuroprotection (e.g., Poulton & Muir, 2005; Tillerson, Caudle, Reveron, & Miller, 2003; Ridgel, Vitek, & Alberts, 2009).

On the inadequacy of physical activity in treating DLB

It is absolutely common knowledge that concentration, that is, sustained attention, is the key element to connecting the IPS to the body. In order to work the body, the IPS must be alert. It is the IPS that wills the body into action. During physical activity it is necessary to pay attention to the movements that have to be performed and to note how the body reacts. Sloppy, haphazard movements are not allowed, controlled movements are mandatory and must be performed with the utmost control. Besides, physical activity requires dedication, commitment and allegiance. Despite the already mentioned benefits of physical activity, clinical practice teaches that it is not an easy task to convince an elderly person diagnosed with DLB to engage in such activity. It takes a lot of convincing and considering some of the already mentioned symptoms of DLB, such as cognitive fluctuations, EPS, attention deficits, and apathy, it becomes clear that there is an enormous probability that such individuals will not set out on such an enterprise.

BPSD are those non-cognitive symptoms that also characterises DLB, that is, beyond cognitive symptoms that characterises different sorts of dementia, there are some manifestations, such as apathy, that are extremely important because such manifestations determine not only the differential diagnoses and the prescribed pharmacotherapy but also institutionalisation and the stress of close relatives. Apathy, for instance, is a serious impediment to the integration of the person in physical activity programs. Apathy is evident by the total lack of interest, initiative and activity in various aspects of daily life. It is plain the decrease in emotional response, facial expression and inflection of voice. Apathy does not mean sadness and it is never accompanied by unhappiness, despair or negativism, in other words and in a simple manner, apathy is a characteristic state of feeling of "*I could not care less*".

Psychosocial intervention is a process of active change which aims at capacitating

the elderly diagnosed with DLB to reach a level of optimal functioning. Of course the emphasis differs according to the needs of the individuals and their families, the type of problem and the degree of impairment. The whole process involves using some strategy or technique that allows the person and closest relatives to handle effectively BPSD and cognitive symptoms of the disease in order to reduce debilitating consequences and make life less complex.

On research on music therapy

Considering that physical activity does not present itself as a viable therapeutic option for elderly people diagnosed with DLB, music therapy would potentially offer an alternative psychosocial therapy without side effects and with clear implications to the individual's quality of life. Research on music therapy however is still in its early stages and have to come up with better methodology. A recent Cochrane Review (Vink, Bruinsma, & Scholten, 2011) on the effects of music on older people's BPSD concluded that there are still very few studies, these are short-term studies, and their designed methodology is fragile, easily broken or damaged or destroyed, vulnerably delicate, lacking substance or significance. Besides, the way results are presented in these studies does not allow for crystal clear conclusions. The Cochrane Review concludes that presently no useful conclusions can be drawn on the effects of music on dementia, thus no conclusion whatsoever can be draw on the effects of music on DLB.

Holmes, Knights, Dean, Hodkinson, and Hopkins (2006) tried to design and implement a rigorous scientific methodology in order to evaluate the effects of music on the apathy symptoms of elderly people diagnosed with dementia. Apathy, as previously mentioned, is a BPSD and one of the diagnostic indicators of DLB. These researchers worked with 32 elderly people that had been diagnosed with differing sorts of age-associated dementia and exhibited severe (56% of the group) and moderate dementia. All of the individuals presented this BPSD - apathy - and they were all randomly submitted to 30 minutes of prerecorded music, 30 minutes of live music and 30 minutes of total silence. Prerecorded music and live music were exactly the same - a mix of elderly people's (from 80 years of age) favourite songs. Each individual was tape recorded in one occasion for each of the three experimental conditions in the same session of one hour and 30 minutes. All 30

minutes films were labelled randomly with a code and the specific experimental condition was removed for visual observation only.

The films were then analysed every three minutes using Dementia Care Mapping (DCM) in the blinded evaluation of each participant's quality of involvement in each intervention. DCM is a validated instrument of observation with high inter-rater and test-retest reliability. It examines 26 different activities where each person's interaction with a given activity is rated on a six-point Likert scale. The scale (-5, -3, -1, +1, +3, +5) ranges from a score of -5 to +5. The former score indicates that the individual is experiencing extreme apathy with that activity, or, in other words, experiencing an exceptional ill-being, and the latter score meaning that the individual is experiencing a high level of engagement, self-expression or social interaction with that activity, or, in other words, experiencing an exceptional well-being.

Results showed that live music was significantly ($p<0.01$) associated to a more positive level of engagement, self-expression or social interaction with the activity, independently of dementia's degree. In other words, live music was positively associated to diminished apathy during its presentation.

Holmes et al. (2006) examined the participants' engagement (from highly involved to severe ill-being) in an expressive or creative activity. Live music was significantly ($p<0.01$) superior to prerecorded music. It is interesting to observe that the effects of prerecorded music compared to the effects of periods of silence on the participants' level of engagement, self-expression or social interaction were not significantly different.

In conclusion, music does seem to work, at least as a short-term psychosocial intervention, in the treatment of the apathy in moderate and severe age-associated dementia, but it must be live music. Live music was significantly ($p<0.01$) associated to a more positive

level of engagement, that is, live music was positively associated to diminished apathy during its presentation. Prerecorded music certainly brings no harm but also did not provide any short-term benefits.

There are many differing procedures from which information can be acquired, however only one of those procedures is the scientific method. Scientific method provides information that is as much as possible based on reality. Through the scientific method it is possible for researchers to acquire information free from personal belief, perception, values, attitudes and emotion. Such information can be obtained testing empirically ideas and beliefs according to a specific procedure open to public inspection. Information obtained through the adoption of the scientific method is worthy of reliance or trust because it is knowledge based essentially on objectively observed evidence. Controlled verification is an absolutely essential process in science and without it the relationship among events cannot be identified. Replication means that observations made by one researcher can be reproduced by other researcher, that is, the same results must be found if the same study is carried out again, because if a set of observations can be made exclusively by one investigation, such information is useless.

In order to present results that lead to crystal clear conclusions the method followed by the researcher must be clearly reported. The researchers must report exactly how the study was conducted. Research into the long-term effects of live music on the apathy of elderly people diagnosed with dementia in general and DLB in particular is urgently needed because it represents a nonpharmacologic, psychosocial intervention that has potential benefits in the management of BPSD and cognitive symptoms.

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