

The Plasticity of Brain Networks as a Basis for a Science of Nervous System Rehabilitation

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Abstract

The paper overviews physiologic efficiencies to provide justification for moving away from a medical model of rehabilitation using a binary conceptualization of impairment and moving towards a linear model of optimization and human efficiencies. While the clinical and neuropathological evaluation of neurological compromise has traditionally concentrated upon the focal distribution of brain disease, ignored have been the changes in the complex connections linking brain areas crucial for cognition and optimized human performance. The paper reviews the nature of nervous system plasticity, from a systems standpoint using language development and bilingualism as well as music and the brain as examples of optimized network functioning.

Keywords: Plasticity; Functional Disconnection; Rasmussen's Syndrome; Cognitive Efficiency, Optimization; Bilingualism; Music Therapy

Introduction

We possess as neurological adults, a high degree of localization of function, with now over 150 years since Broca, we still subscribe to the notion consistent with the model that dysfunction or damage to specific regions of the brain and nervous system should result in specific damage and deficits in the behavior and function of individuals. Unfortunately, that is not enough to explain the capacity for plasticity, regeneration, spontaneous recovery, and optimization in neurological terms and certainly not in its translation in clinical rehabilitation.

Among the difficulties we face in the application of rehabilitation science in practice is less the need to understand how the nervous system functions, but rather how it recovers from dysfunction, how can we effectively evaluate function, dysfunction and recovery, and a how to provide a rational basis for making economic decisions about in which method or methodology to invest.

We have learned what happens to the nervous system when infants learn to talk, sit down and stand up, toddle, walk, and eventually run. We know how to teach a child how to grasp a pencil and write, we also understand from the primitive reflex "operating system," how it is that those reflexes combine to form complex behavior and how those behaviors break down after a stroke. Complex behavior over normal development and experience combines activity in various brain regions that after stroke breaks down to result in more compartmentalized functioning. We can see retained function in some areas and dysfunction in others that would normally be combined in the neurologically intact adult, such as in alexia without agraphia and with a color-naming deficit. In such a case, an individual could not read, but could write, but could not read what he or she had written (for a further description, see [1,2]). The use of medical rather than a statistical "production management" models in examining human function creates for binary thinking that allows us to evaluate human performance in the context of function-dysfunction, diseased-non-diseased, impaired-non-impaired, but not contextualized in a linear fashion in the form of optimization and efficiencies of function with one level of that scale being represented by elite sports performers to the brain-spinal cord injured, and on the opposite side of the spectrum to those in a locked-in state, and the "brain dead." [3,4].

A two-year olds' motor and cognitive function is developmentally

appropriate but neurologically highly inefficient. The task of infancy and child development is to render the individual more optimized.

When a two and a half-year old descends a staircase, he examines each step and progresses one step at a time. An older child, who has already learned how to automate that descent like an adult, examines the first step, pays no further conscious attention and descends automatically. In fact, the function of most integrated behavior is to automate as much of our responses to the world as possible as the information content from our environment is so high and our cognitive system's capacity to effectively interact with the environment is so limited [2,5,6]. The function then of early development is training to be able to integrate what should normally be independent reflex-based processes into meaningful systems with those systems being less reliant on specific brain regions for their control and more so on the networks that are created to optimize the processes for effective performance.

Optimization Through Neural Connectivities and Less on Localization

It is for this reason, that one of the primary functions of neurological development of the nervous system is the integration of developing systems so that function will be localized for more efficiency. But that is not to say that the system must work by localized control [7,8]. For example, the languages that are learned in early childhood prior to the development of Broca's and Wernicke's areas, with their nominal control of expressive and receptive language respectively, are learned fast as a consequence of the exuberant neuronal connectivities present in early childhood development as evidenced in Figure 1.

These abundant connectivities in childhood allow for the rapid acquisition of knowledge. The childhood system of exuberant

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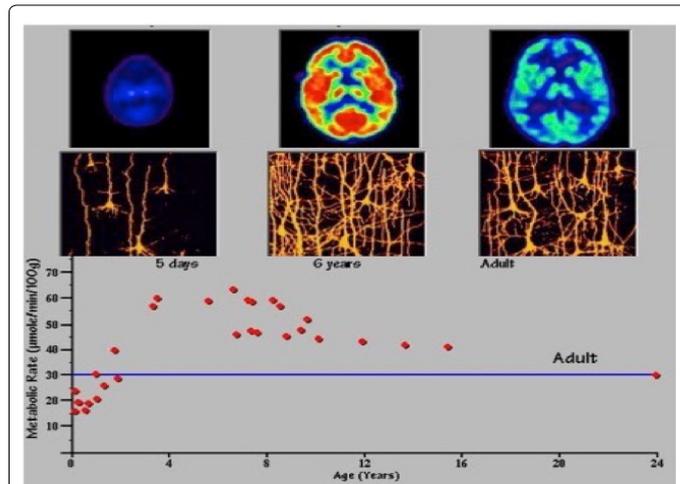


Figure 1: Elevated CMRGlC during 3-10 yrs. corresponds to era of exuberant connectivity needed for the energy needs of neuronal processes. This is greater by a factor of 2 compared to adults. PET scans show the relative glucose metabolic rate. We also see the complexity of dendritic structures of cortical neurons consistent with the expansion of synaptic connectivities and increases in capillary density in the frontal cortex.

connectivities renders the nervous system less optimized than the adult brain-state and its resultant localization of function. When that now optimized localization of function has developed, the number of potential connectivities is significantly reduced. Specialization of cortical regions optimizes the system but does so by concentrating the networks in a circumscribed area allowing for more effective temporal as well as spatially represented responses as represented in Figure 2. In short, more potential connectivities in early childhood will lead to greater automatization of skill-development and localized function in the normal adult and less of an ability of the adult to acquire information with as much ease as in early childhood.

Specialization, however, is a result of a long process of development and training. One, for example may have a neonate born with anencephaly and function quite normally. Rasmussen's syndrome with its early onset, lateralized status seizures requiring hemispherectomy, results in dysfunction significantly less than one would expect in the adult. Figure 3(A) represents the CT of Terry Schiavo who was

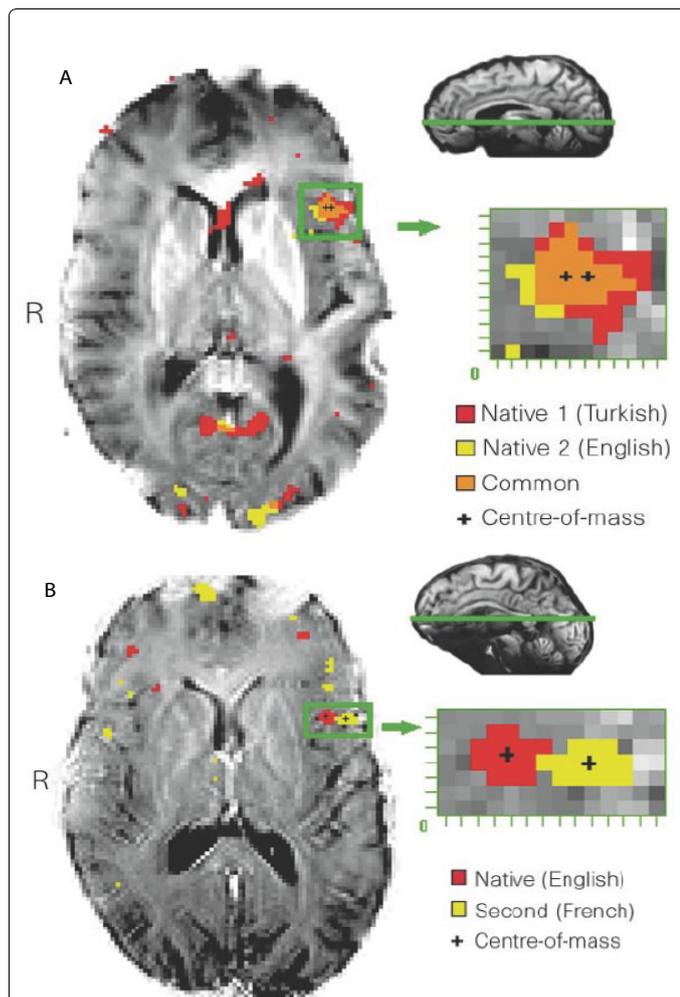


Figure 2: Bilingual brains (A) early exposure and (B) late second language exposure.

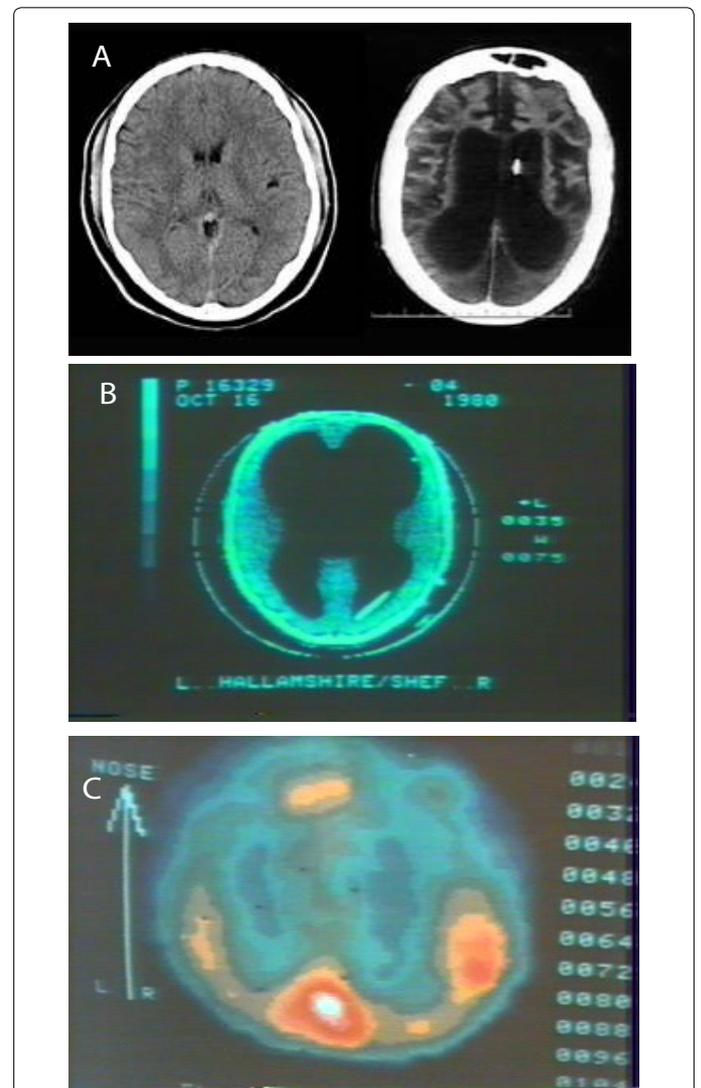


Figure 3: (A) CT of normal (l.) and that of the brain of Terry Schiavo (r.) when the latter was in Persistent Vegetative State. (B) CT of normally functioning teenager with congenital hydrocephalus and a CT similar to that of the patient. (C) Regional Cerebral Blood Flow image of individual in (B) while performing language-based cognitive tasks.

rendered in a Persistent Vegetative State after childbirth due to anoxia and Figure 3(B) represents a CT of the brain of a congenitally anencephalic of normal intellectual ability as an adult. Figure 3(C) represents the individual's regional cerebral blood flow (rCBF) while performing mental arithmetic. Clearly traditional localizationist views are irrelevant in this case where the CTs of Terry Schiavo and the normally functioning anencephalic-from-birth individual are not significantly different. All that differs is the age of onset of the trauma and that then speaks to the nature of functional networks being more important than localization of function.

An Example of Language: Localization, Optimization, and Connectivities

A neuroanatomical conceptualization is a non-starter for rehabilitation practice. It is important to understand that what we

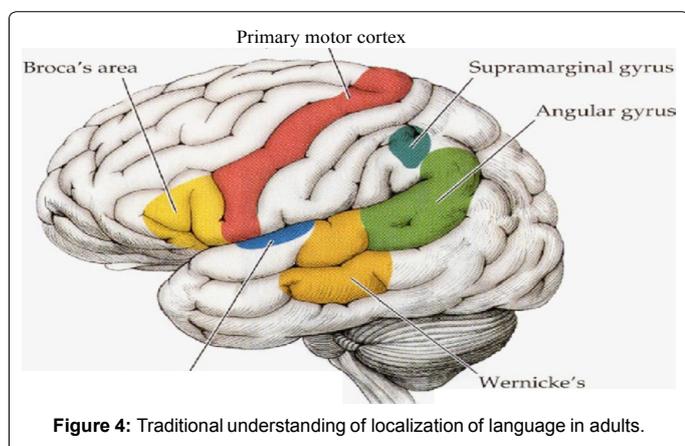


Figure 4: Traditional understanding of localization of language in adults.

are really attempting to achieve both in rehabilitation as well as in understanding the neurological basis of cognitive and motor improvement after trauma or stroke is not which brain area controls a given cognitive function, but how efficiently brain regions cooperate with each other. While not the scope of this paper to provide a detailed overview of this principle, the reader is invited to review these concepts more comprehensively elsewhere [5,6].

Figure 4 presents a traditional view of the localization of language function in the adult brain and Figure 5 represents the nature of network processing of language not circumscribed to a particular locale but rather to an organization of networks for optimized performance. Figure 5 demonstrates multiple self-organizing stream models of receptive language functions organized in simultaneously active networks. Figure 6 then takes the understanding of network processing and demonstrates a non-localized view of language processing measured by tractography.

A concept of “cortical efficiency” that we have earlier described [4,9-11] indicates that higher ability in a cognitive task is associated with more efficient neural processing and not necessarily with a particular brain region that is involved in that processing. Intuitively, we would expect higher performance to correlate with more activity. For the cerebral cortex, however, the contrary is the case. Higher performance in several tasks, including verbal [12], numeric, figural, and spatial reasoning [13,14] is consistent with the reduced consumption of energy in several cortical areas. This phenomenon has also been studied with EEG techniques in different frequency bands. The amount of a background power (7.5–12.5 Hz) decreases during cognitive activity compared with the resting state. This decrease has been observed to correlate with higher performance in subjects with higher IQ scores [11] or with higher performance after training, indicating a more efficient

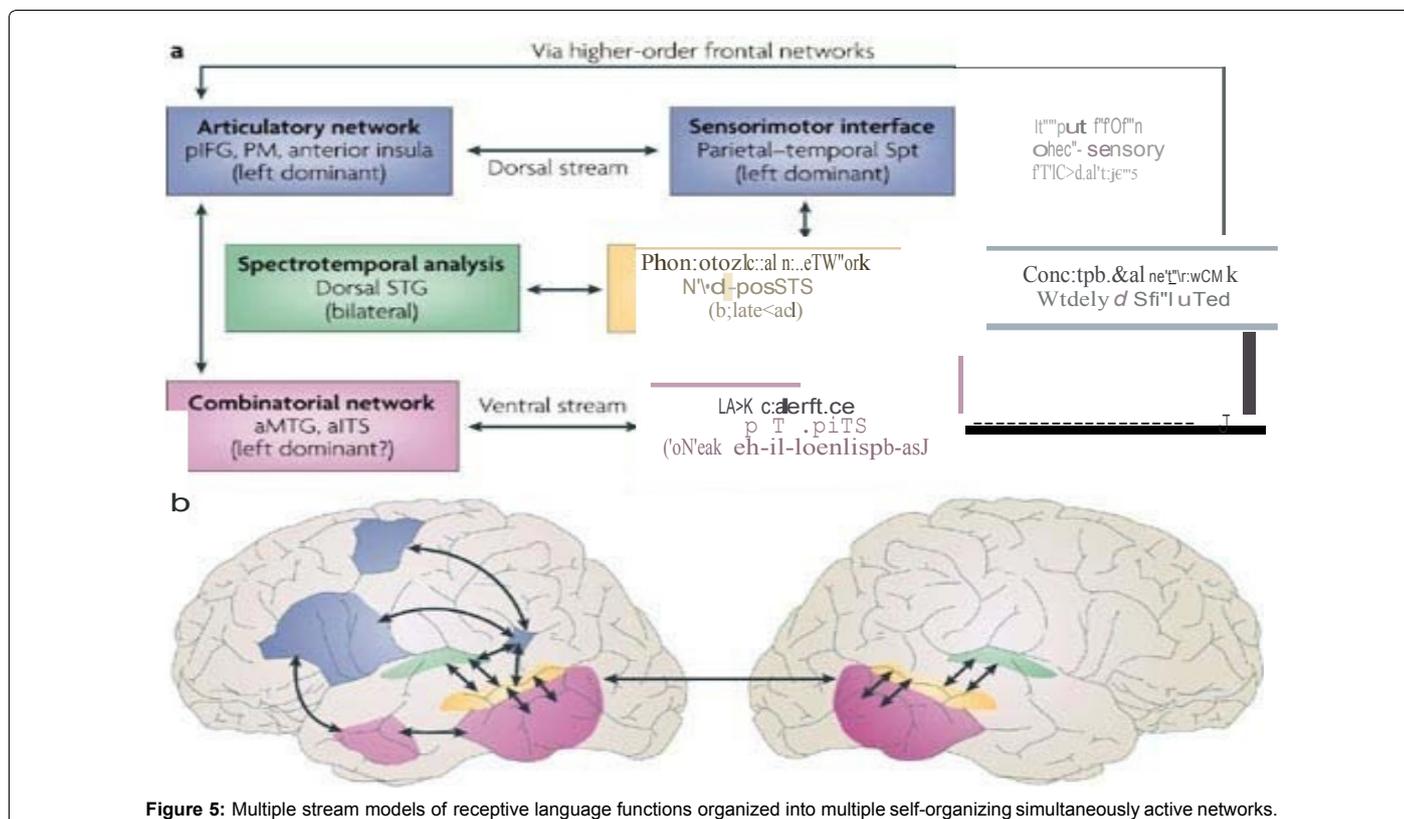
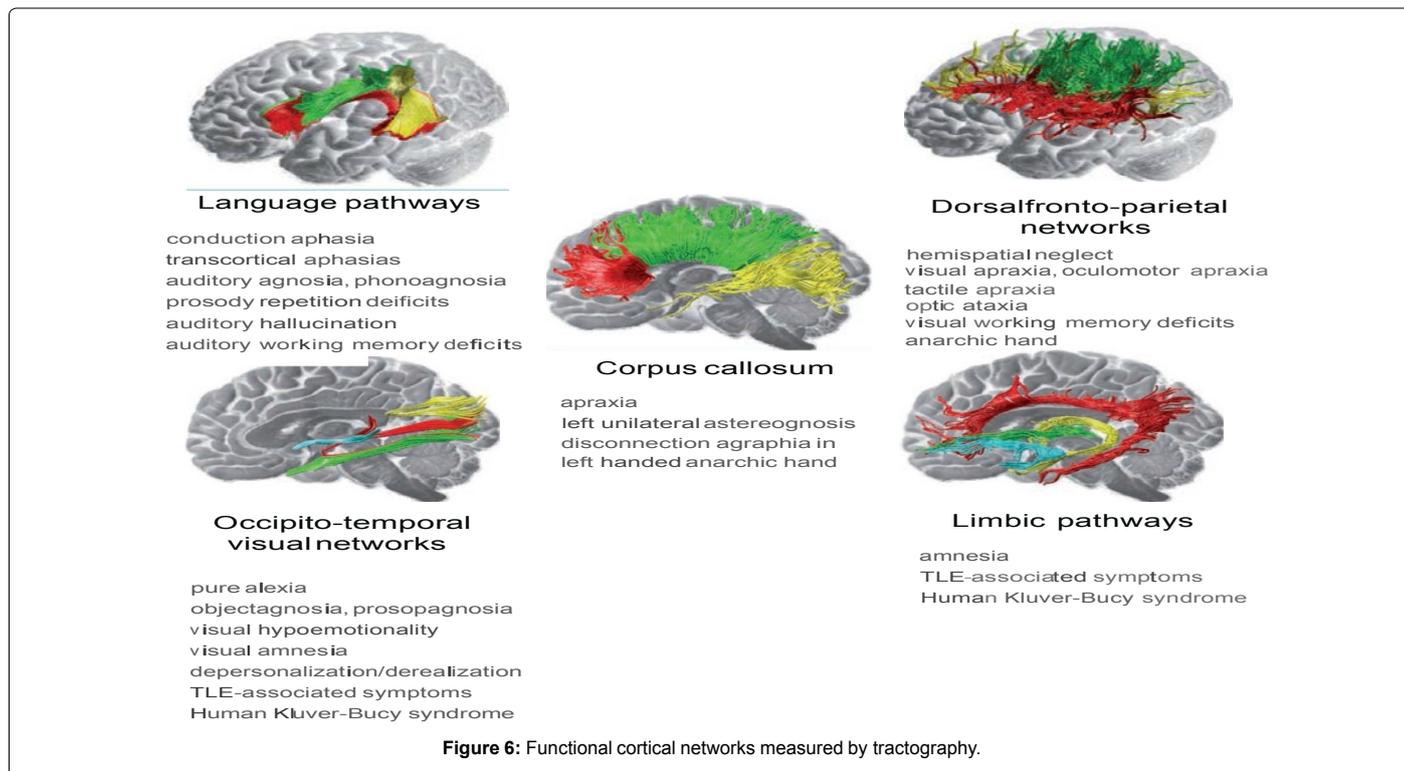


Figure 5: Multiple stream models of receptive language functions organized into multiple self-organizing simultaneously active networks.



processing strategy for a cognitive task [15]. Most of these studies from the literature have focused mainly on the domain of intelligence, but relatively little attention to the investigation of task performance in second language learners or bilinguals.

In an EEG coherence study on second language (L2) processing/bilingualism, an extension of the “cortical efficiency” paradigm was examined. Coherence, the amount of shared activity between any two electrode pairs and taken over the entire scalp surface, gives an index of inter-regional communication effectiveness. The acquisition of an L2 is equivalent to the training of a cognitive-behavioral skill, and some individuals respond to this training more efficiently than others. If an L2 is acquired before a certain age or critical period, native speaker proficiency is achieved easily (early bilingualism).

If training starts later in life, the proficiency level achieved depends on the amount of training, exposure, and on some kind of “predisposition” or aptitude of the individual. Whereas, in general, L2 processing involves the same language-specific cortical areas (with left hemisphere preference) as native language (L1) processing (*cf.* review [16]), neuroimaging studies have repeatedly shown that lower L2 proficiency is correlated with more widespread cortical activity. Perani et al., [17] were consistent with the “cortical efficiency” concept, but not explicitly investigate it.

Reiterer and colleagues [18] applied this concept in studying late bilinguals/second language learners, comparing, with EEG recording techniques, the recruitment of cortical areas during L2 processing in two groups of individuals differing profoundly in L2 proficiency (although both had started to learn L2 at the same age).

In using coherence analysis or the amount of sharing between any two wave

trains and thus reflective of brain integration of functioning and efficiency, the coherence brain maps (exemplified in Figure 7) revealed

more pronounced and widespread increases in coherence in the α -band (8–10 Hz) in low-proficiency than in the high-proficiency L2 speakers. Surprisingly, this difference was obtained also during L1 processing and corroborated for both languages by multivariate permutation tests. These tests revealed additional differences between the low- and the high-proficiency group also for coherences within the β 1- (13–18 Hz) and the β 2- band (18.5–31.5 Hz).

The point is that greater activity is demonstrated with less proficiency and vice versa. The function of childhood neurological development is to facilitate the dynamic creation of specialized cortical function. As this function can be changed, it is therefore plastic. This localization of function is not the explanation of how cognitive processes are controlled in the brain, but rather the end-result of training. The efficiency of cognitive function is directly related to the effectiveness of network organization in the neocortex and that can now be measured. Fewer brain regions necessary to accomplish a single task in one individual compared to another for the same task is a measure of efficiency.

Brain Networks: Measurement of Changes in Brain State through Therapeusis

The networks, active during learning and problem solving of all kinds, are plastic and can be changed as a direct consequence of experience and training. In attempting to apply graph theory concepts to child and adolescent neurocognitive performance to create a fundamental change in the educational training and evaluation paradigm, we can characterize the organization & development of large-scale brain networks using graph-theoretical metrics as represented in Figure 8 below. Early and intensive training in keyboard and string players and the requirement for increased and faster inter-hemispheric exchange in order to perform bimanual complex motor sequences lead to structural changes in the callosal anatomy. We know that there exist

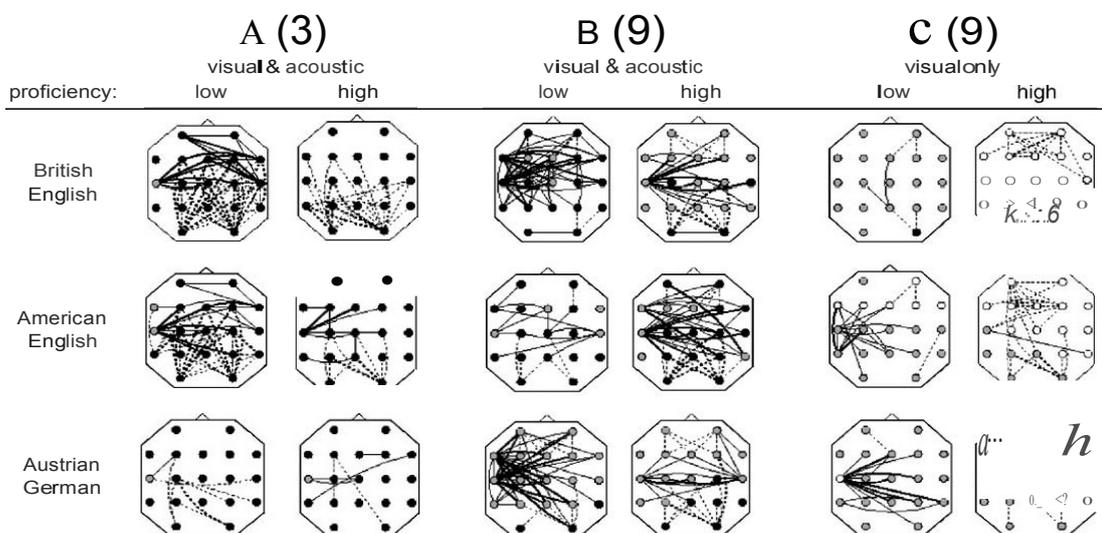


Figure 7: Significant coherence differences (the amount of shared activity between EEG electrode sites) in high-proficiency versus low-proficiency bilinguals relative to the default condition (silence, noisy screen) in the δ frequency band (0.5–3.5 Hz) during processing of visual and acoustic signals (A), and in the θ -band (4.0–7.5 Hz), during processing of visual and acoustic signals (B), and of visual signals only (C). The text was either in British English (1st row), American English (2nd row), or in Austrian German (3rd row). (cf. [18]).

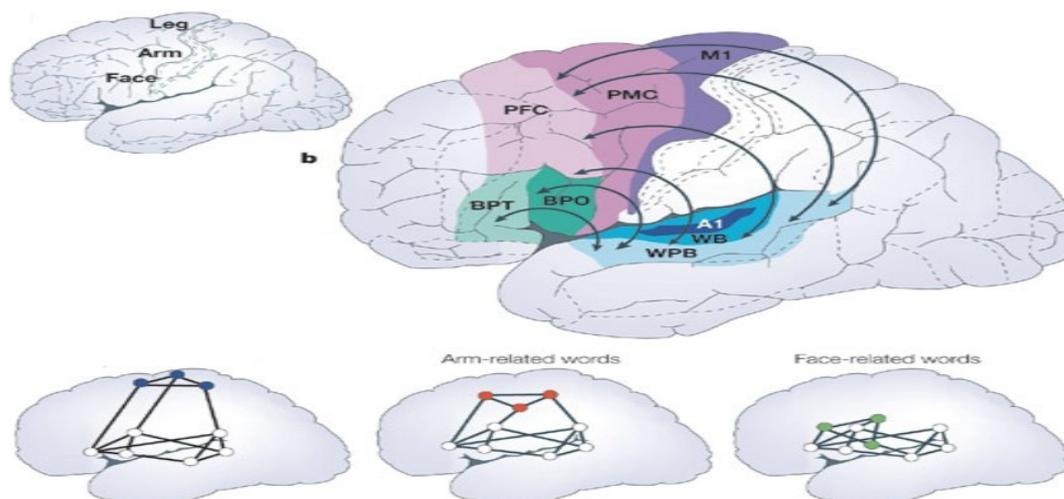


Figure 8: Grounded meaning indicates that the meaning of words and sentences are “embodied”.

differences in the brains of musicians and non-musicians exemplified in Figure 9. [19–21] The examination of the differences in the brains of musicians and non-musicians provides an ideal model to compare and examine functional and structural brain plasticity as musicians continuously practice complex motor, auditory, and multimodal skills. We also know that music training in children results in long-term enhancement of visual-spatial, verbal, and mathematical performance. [5,22]. It has been found that the brains of adult musician and non-musician (Figure 9) show differences in the size of the anterior and mid-body of the corpus callosum. In particular, as exemplified in Figure 9(D), areas of significant difference are noted in voxel size over a fifteen month period when comparing instrumental against non-instrumental control children. The changes are mostly noted in the mid-body portion of the corpus callosum of parts that contain primary sensorimotor and premotor fibers. Figure 9(C) demonstrates

the subdivisions and locations of inter-hemispheric fibers that connect motor and hand regions located in both the right and left hemispheres. Schlaug [24] compared thirty professional musicians and matched non-musician controls and found that the anterior half of the corpus callosum was significantly larger in musicians. He noted that musicians possessed a significantly larger anterior corpus callosum with early musical training as compared to musicians who started their training later and both compared to controls.

Previous anatomical studies found a positive correlation between mid-sagittal callosal size and the number of fibers crossing through the corpus callosum. The anterior part of the corpus callosum contains mainly fibers from frontal motor-related regions and prefrontal regions, [25] and the anterior corpus callosum matures the latest of all callosal sub-regions. Therefore, this anatomical difference in the

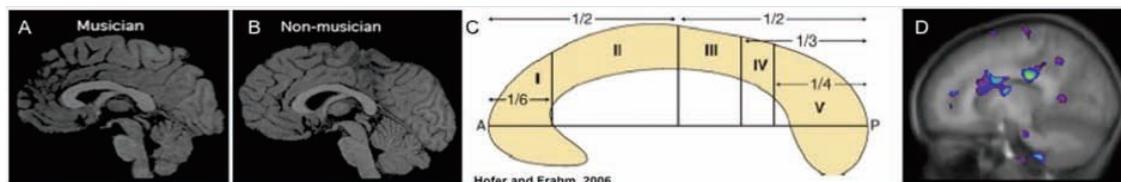


Figure 9: Corpus callosal differences in the brains of adult musicians and non-musicians using the Hofer & Frahm [23] classification system. (A) Brains of adult musicians and (B) non-musicians demonstrate differences in the size of the anterior and mid-body of the corpus callosum, (C) demonstrates callosal subdivisions and locations of interhemispheric fibers that connect motor and hand regions of the right and left hemispheres and (D) represents areas of significant difference in voxel size over 15 months comparing instrumental and non-instrumental control children that are superimposed on an average image of all children. The changes found in the mid-body portion of the corpus callosum of parts that contain primary sensorimotor and premotor fibers.

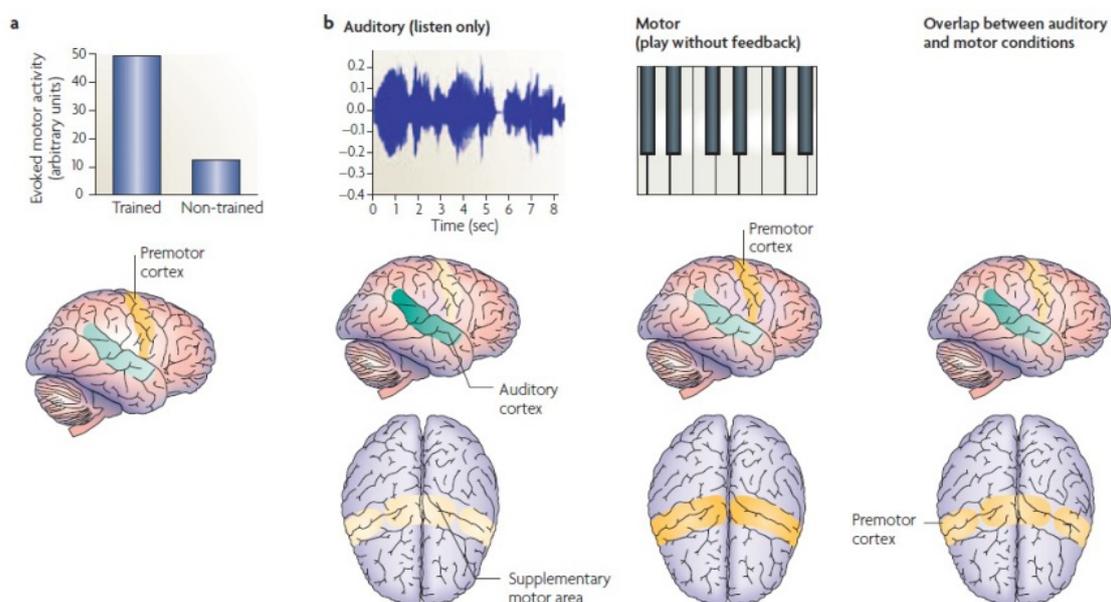


Figure 10: A) People with no music training learn melody on a keyboard. After hearing the learned piece, they exhibit expected activity in auditory cortex, and premotor areas. No effect is noted when listening to untrained melody (bar graph). B) Brain activity in musicians while listening to piece they could play (l. column) with activity playing same piece with no auditory feedback (Mid. column). Significant overlap is noted in auditory and premotor regions in each condition (r. column). Auditory and motor systems interact during perception & production.

mid-sagittal area of the corpus callosum has to be seen in the context for a requirement for increased inter-hemispheric communication subserving complex bimanual motor sequences in musicians. These reported brain changes clearly exemplify environmental influences on brain development and should be viewed in the context of both human development and rehabilitation.

There is much evidence supporting the notion that plastic changes can be induced in the functional organization of the human sensorimotor cortex following sensory stimulation or following the acquisition of new motor skills. These functional changes after skill acquisition may be related to microstructural changes such as increased numbers of synapses per neuron, [26] increased numbers of glial cells per neuron, [26] and/or more capillaries [27] as has been shown in animal experiments.

Many parts of the brain participate in music making. Musical sounds are processed in the auditory cortex. Pathways then carry music to areas of the brain that perform and anticipate harmonic and melodic changes, as well as feel, remember and read.

Motor control systems for music production require abilities in timing. Such abilities relate to the organization of musical rhythm,

sequencing, related to playing individual notes on musical instruments, and the spatial organization of movement all resulting in sensory-motor integration. Reviewed in greater detail by Melillo and Leisman [5], we know that cerebellar, basal ganglia, and pre-motor cortex involved patients have impaired ability on perceptual-motor timing tasks, as well as in the computation of movement prediction, and in the control of movement trajectories.

We know that motor timing is not controlled by single region of the brain but by regional networks that control movement. The high-level control of sequence execution at the least involves the basal ganglia and the pre-motor cortex, whereas the cerebellum controls fine-grain correction of individual movement.

Motor sequencing, on the other hand, according to Melillo and Leisman [5] implicates the supplementary and pre-supplementary motor areas, cerebellum, parietal, and pre-frontal cortical areas. The cerebellum integrates individual movements into unified sequences. The pre-motor cortex is involved in tasks requiring the production of complex sequences contributing to motor prediction.

Finally, spatial organization involves the parietal sensorimotor and pre-motor cortices that control movements when the integration of

spatial, sensory and motor information is required. Figure 10 indicates that when individuals with no musical training learn a melody on a keyboard, upon hearing the learned piece, they exhibit the expected activity in auditory cortex and premotor areas. On the other hand, no effect is noted when individuals listen to a melody in which there has been no training. When examining brain activity in musicians while listening to a piece that they could play, we can note a significant overlap of activity in auditory and premotor regions. The auditory and motor systems interact during music perception and production.

We know [28] that musical training is supported by brain plasticity. We can see, for example, that in Figure 11 that training affects the arcuate fasciculus, and auditory- motor tract, enhanced by music training.

Discussion

Differences in the brains of musicians and non-musicians are evident from what we have seen. The musician–non-musician study is an ideal model to compare and examine functional and structural brain plasticity as musicians continuously practice complex motor, auditory, and multimodal skills. Music training in children results in long-term enhancement of visual–spatial, verbal, and mathematical performance. [22,29]. The learning of complex sequences requires adequately functioning executive processes (e.g. those involved with error monitoring or motor program structuring). Structural complexity remains the same for any sequence, be it with music or any other task.

Music affords a system to both study and remediate the acquisition of sequencing behaviors and their impairment. Activations at varying levels of complexity have demonstrated overlap in the supplementary motor cortex, among other areas. [30] Areas of overlap have also been noted for the cerebellum, basal ganglia pre-motor cortex, thalamus, ventro-lateral pre-motor cortex, and precuneus, with increased activations at increased levels of complexity. Increases in musical complexity have concomitant increases in neural recruitment. [22,29] The available data supports a core circuit that includes the supplementary motor cortex, cerebellum, and premotor cortex in sequencing.

Brown and colleagues [31] among others [30] have noted that music’s effect on the brain is similar to the brain’s activation by language stimuli. This serves as a rationale in the employment of music as a therapeutic aid after nervous system trauma and in its rehabilitation. Exemplified in Fig 12 are areas for generating melodic phrases that appear in Brodmann’s areas (BA) 45, BA 44, the temporal planum bilaterally, the lateral BA 6, and the pre-supplementary motor area. Areas for generating sentences were of course noted in the bilateral posterior, superior, and mid temporal cortex, (BA 22, 21), BA 39, bilateral, superior, and frontal (BA 8, 9), the left inferior frontal (BA 44, 45), the anterior cingulate, and the pre-supplementary motor area. Both tasks showed activations in the same functional brain areas, including the pre-motor cortex, supplementary motor area, Broca’s area, anterior insula, primary and secondary auditory cortices, temporal pole, basal

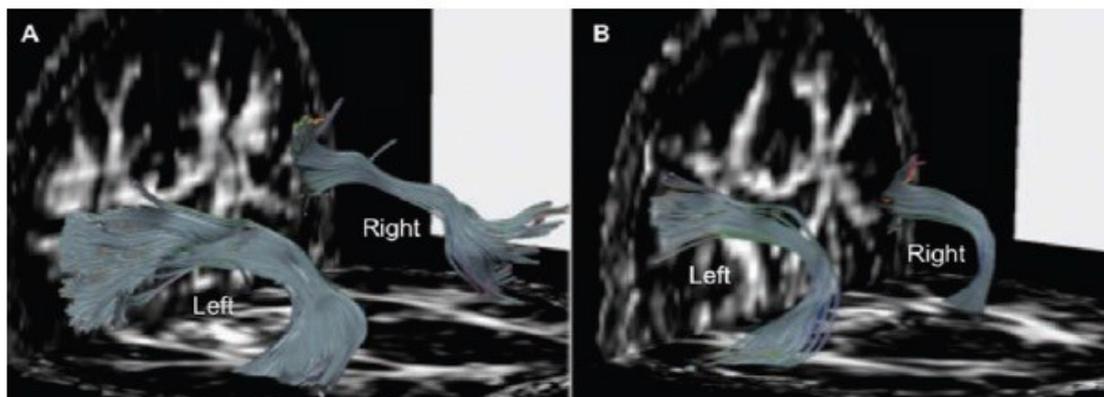


Figure 11: The (A) arcuate fasciculus [AF] of healthy 65-year old musician and (B) AF of a 63-year-old non-musician, matched for handedness, gender, and IQ. The musician has a larger AF on the left as well as on the right hemisphere than the non-musician. The data supports the notion of plasticity of the AF in those undergoing instrumental training or therapy using tasks that involve auditory- motor mapping, a task that musicians do throughout life (cf. [28]).

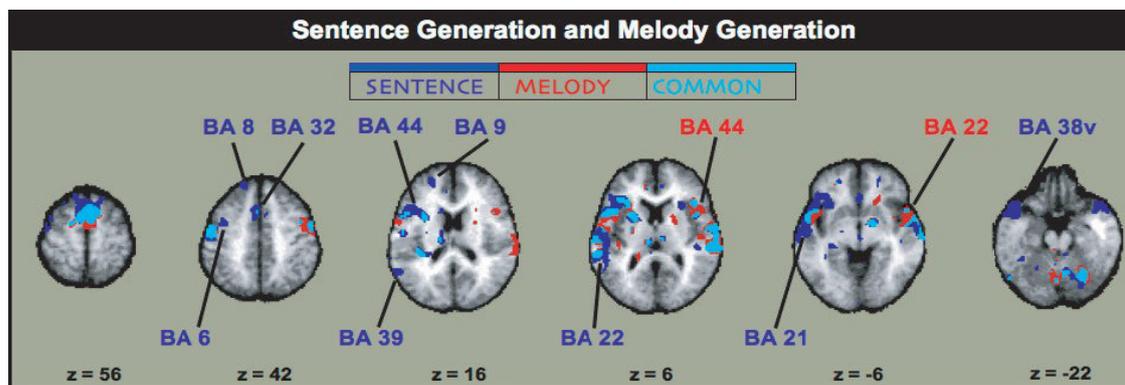


Figure 12: Activation to melody (red), sentence generation (blue), and common to both tasks (cyan).

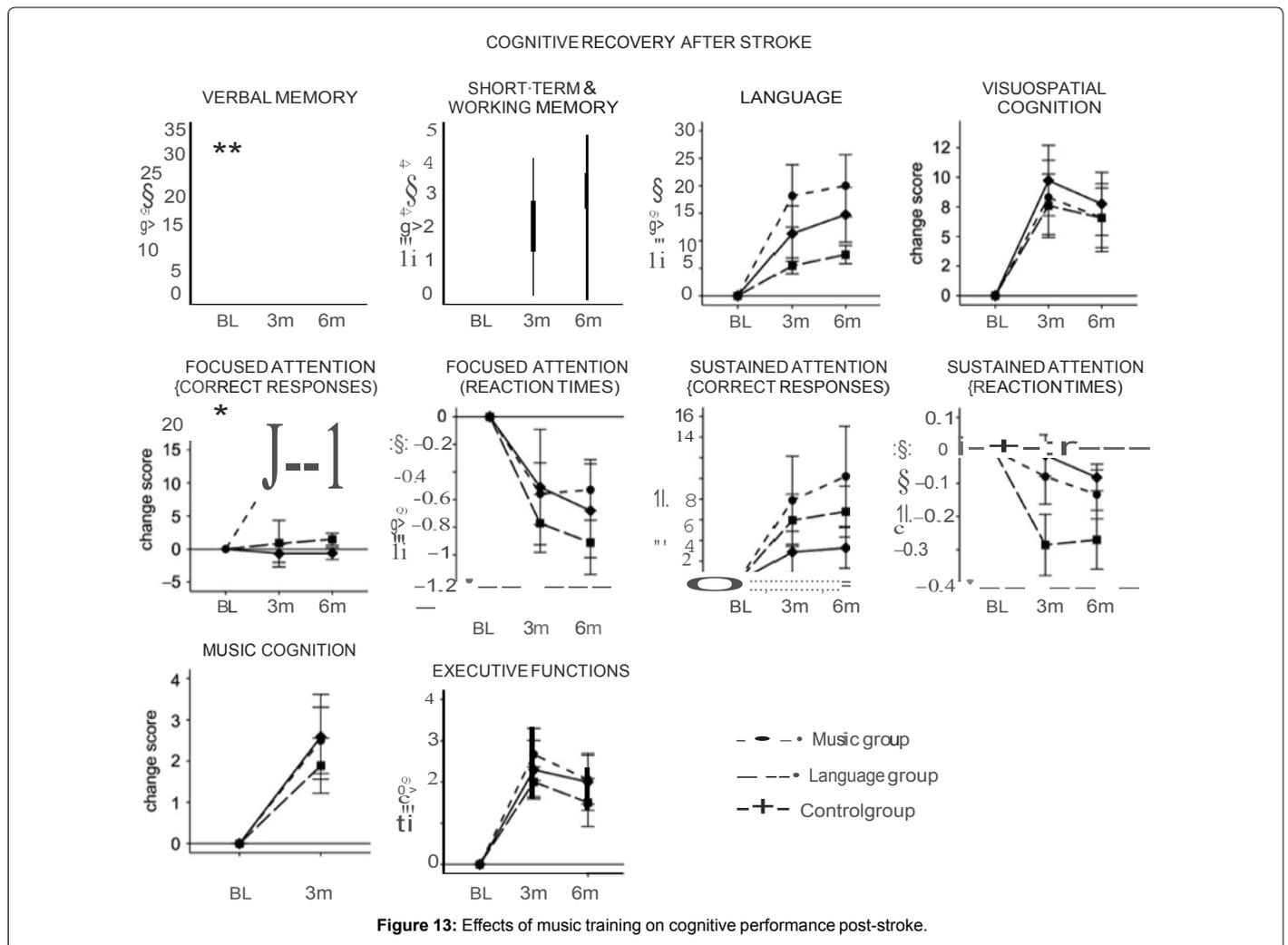


Figure 13: Effects of music training on cognitive performance post-stroke.

ganglia, ventral thalamus, and posterior cerebellum. The differences between melodic and sentence generation are seen with lateralization tendencies, with language tasks favoring the left hemisphere. Data also supports the notion that component sharing, parallel processing, and adaptive coding explain results with shared, parallel, and distinctive features of the neural systems supporting both music and language. Music and language show parallel combinatory generativity for complex sound structures (phonology) but distinctly different informational content (semantics).

The result of plasticity evidenced in musical training is that there exists a rational basis for the employment of music in general cognitive growth and in the rehabilitation of cognitive skills in individuals with brain impairment (see Figure 13), and that training facilitates changes in brain state in children, adults, and in the neurologically impaired.

References

1. Sroka H, Solsi P, Bornstein B (1973) Alexia without agraphia with complete recovery. Functional disconnection syndrome. *Confin Neurol* 35: 167-176.
2. Leisman G (1976) The neurophysiology of visual processing: Implications for learning disability. In: *Basic visual processes and learning disability*. Charles C Thomas, Leisman G (Ed.) Springfield, IL, US.
3. Leisman G, Koch P (2009) Networks of conscious experience: computational neuroscience in understanding life, death, and consciousness. *Rev Neurosci* 20: 151-176.

4. Gilchrist JA (2011) A method for quantifying visual search scanpath efficiency. *Funct Neurol Rehab Ergon* 1: 181-196.
5. Melillo R, Leisman G (2010) *Neurobehavioral disorders of childhood: An evolutionary perspective*. Springer, New York, USA.
6. Leisman G (2011) Brain networks, plasticity, and functional connectivities inform current directions in functional neurology and rehabilitation. *Funct Neurol Rehab Ergon* 1: 315-356.
7. Leisman G, Rodríguez-Rojas R, Batista K, Carballo M, Morales JM, Iturria Y, Machado C (2014) Measurement of axonal fiber connectivity in consciousness evaluation. *IEEE 28th Convention of Electrical and Electronics Engineers in Israel*.
8. Leisman G (2012) Children's language production: How cognitive neuroscience & industrial engineering can inform public education policy and practice. *Forum on Public Policy: A Journal of the Oxford Roundtable*.
9. Ertl JP, Schafer EW (1969) Brain response correlates of psychometric intelligence. *Nature* 223: 421-422.
10. Grabner RH, Stern E, Neubauer AC (2003) When intelligence loses its impact: neural efficiency during reasoning in a familiar area. *Int J Psychophysiol* 49: 89-98.
11. Grabner RH, Fink A, Stipacek A, Neuper C, Neubauer AC (2004) Intelligence and working memory systems: evidence of neural efficiency in alpha band ERD. *Brain Res Cogn Brain Res* 20: 212-225.
12. Parks RW, Loewenstein DA, Dodrill KL, Barker WW, Yoshii F, et al. (1988) Cerebral metabolic effects of a verbal fluency test: a PET scan study. *J Clin Exp Neuropsychol* 10: 565-575.

13. Lamm C, Bauer H, Vitouch O, Gstättnner R (1999) Differences in the ability to process a visuo-spatial task are reflected in event-related slow cortical potentials of human subjects. *Neurosci Lett* 269: 137-140.
14. Vitouch O1, Bauer H, Gittler G, Leodolter M, Leodolter U (1997) Cortical activity of good and poor spatial test performers during spatial and verbal processing studied with Slow Potential Topography. *Int J Psychophysiol* 27: 183-199.
15. Neubauer AC, Grabner RH, Freudenthaler HH, Beckmann JF, Guthke J (2004) Intelligence and individual differences in becoming neurally efficient. *Acta Psychol (Amst)* 116: 55-74.
16. Perani D, Abutalebi J (2005) The neural basis of first and second language processing. *Curr Opin Neurobiol* 15: 202-206.
17. Perani D, Abutalebi J, Paulesu E, Brambati S, Scifo P, et al. (2003) The role of age of acquisition and language usage in early, high-proficient bilinguals: an fMRI study during verbal fluency. *Hum Brain Mapp* 19: 170-182.
18. Reiterer S, Hemmelmann C, Rappelsberger P, Berger ML (2005) Characteristic functional networks in high- versus low-proficiency second language speakers detected also during native language processing: an explorative EEG coherence study in 6 frequency bands. *Brain Res Cogn Brain Res* 25: 566-578.
19. Lee H, Noppeney U (2011) Long-term music training tunes how the brain temporally binds signals from multiple senses. *Proc Natl Acad Sci U S A* 108: E1441-1450.
20. Herholz SC, Boh B, Pantev C (2011) Musical training modulates encoding of higher-order regularities in the auditory cortex. *Eur J Neurosci* 34: 524-529.
21. Schlaug G1, Norton A, Overy K, Winner E (2005) Effects of music training on the child's brain and cognitive development. *Ann N Y Acad Sci* 1060: 219-230.
22. Hofer S, Frahm J (2006) Topography of the human corpus callosum revisited-comprehensive fiber tractography using diffusion tensor magnetic resonance imaging. *Neuroimage* 32: 989-994.
23. Schlaug G (2001) The brain of musicians. A model for functional and structural adaptation. *Ann N Y Acad Sci* 930: 281-299.
24. Pandya DN, Seltzer B (1986) The topography of commissural fibers. In *Two hemispheres—one brain: functions of the corpus callosum*. Lepore F, Ptito M, Jasper HH. (Eds.). Alan R. Liss, New York, NY.
25. Mitterauer BJ (2010) Significance of the astrocyte domain organization for qualitative information structuring in the brain. *Adv Biosci Biotechnol* 1: 391-397.
26. Stefan K, Kunesch E, Cohen LG, Benecke R, Classen J (2000) Induction of plasticity in the human motor cortex by paired associative stimulation. *Brain* 123 Pt 3: 572-584.
27. Wan CY, Schlaug G (2010) Music making as a tool for promoting brain plasticity across the life span. *Neuroscientist* 16: 566-577.
28. Rauscher FH, Shaw GL, Levine LJ, Wright EL, Dennis WR, et al. (1997) Music training causes long-term enhancement of preschool children's spatial-temporal reasoning. *Neurol Res* 19: 2-8.
29. Leisman G, Melillo R, Mualem R., Machado C (2012) The effect of music training and production on functional brain organization and cerebral asymmetry. In: *Art, Science and Technology*. Kravchuk T, Groysman A, Soddu C, Colabella E, Leisman G. (Eds). Domus Argenia, Milano, Italy.
30. Brown S, Martinez MJ, Parsons LM (2006) Music and language side by side in the brain: a PET study of the generation of melodies and sentences. *Eur J Neurosci* 23: 2791-2803.