

OPINION

The musician's brain as a model of neuroplasticity

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Studies of experience-driven neuroplasticity at the behavioural, ensemble, cellular and molecular levels have shown that the structure and significance of the eliciting stimulus can determine the neural changes that result. Studying such effects in humans is difficult, but professional musicians represent an ideal model in which to investigate plastic changes in the human brain. There are two advantages to studying plasticity in musicians: the complexity of the eliciting stimulus — music — and the extent of their exposure to this stimulus. Here, we focus on the functional and anatomical differences that have been detected in musicians by modern neuroimaging methods.

The size and temporal organization of cortical representations of stimuli are continually shaped by experience^{1,2}. Animal studies over the past 20 years have gone a long way towards explaining some of the rules of cortical plasticity. For example, it has been shown that training to make fine-grained temporal judgments yields an expansion of the bandwidth or receptive field in both the auditory and somatosensory modalities, whereas tasks that require fine-grained frequency or spatial tactile discrimination lead to a decrease in the receptive-field size of cortical neurons^{1,3}. This effect has been explained by Hebbian learning rules, whereby synapses are driven to change by temporally coherent inputs in a competitive neural network. Attention to the sensory input is very important in driving experience-

related plasticity, as is its behavioural significance^{3,4}. Animal research has also revealed neuroplasticity at the molecular, synaptic and macroscopic structural levels^{5,6}. Although animal models are useful for studying the cellular and molecular mechanisms of plasticity, the typical laboratory animal is deprived of normal stimulation and might, therefore, be a special case. Moreover, animal models are limited in the range of stimuli that are used, in the behavioural manipulations that are associated with these stimuli and in the duration of

training. In addition, it is far from clear how the mechanisms that govern synaptic plasticity at the cellular level are related to the flexibility of operations seen for large-scale neuronal networks on the one hand, and cognitive processes on the other.

It is therefore important to extend these investigations to the human brain. Significant headway has been made by studying inter-modal plasticity in congenitally blind⁷ or deaf subjects^{8,9}, or by monitoring the effects of limb amputations¹⁰. In this article, however, we are concerned with findings in professional musicians that have been described over the past decade or so. Performing music at a professional level is arguably among the most complex of human accomplishments. A pianist, for example, has to bimanually coordinate the production of up to 1,800 notes per minute (FIG. 1). Music, as a sensory stimulus, is highly complex and structured in several dimensions¹¹, so it extends beyond any of the stimuli that have been used in animal research. Moreover, making music requires

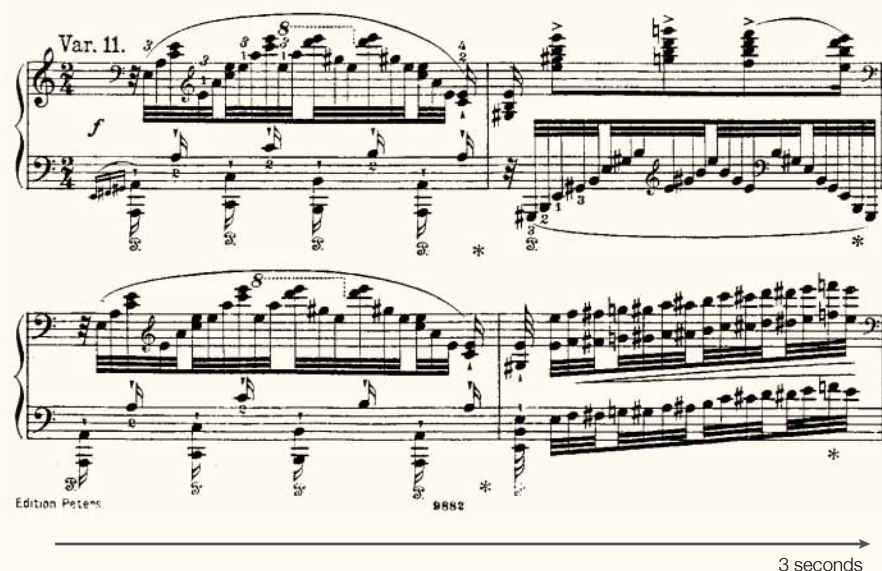


Figure 1 | **Example of a hypercomplex musical score.** Two three-second segments of the 11th variation from the 6th Paganini-Etude by Franz Liszt. The depicted segments require the production of 1,800 notes per minute. Reproduced by kind permission of Peters Edition Ltd.

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the integration of sensory and motor information, and precise monitoring of performance. Finally, the study of musicians might allow us to tease apart the effects of musical training or experience from those of genetic predisposition.

So, the musician's brain might constitute a perfect model in which to study neuroplasticity in the auditory and motor domains. It can also be used to examine the effects of dysfunctional plasticity, as illustrated by musician's cramp, a particular kind of occupational dystonia^{12,13}.

Functional measures of plasticity

In a seminal study in 1995, Elbert and colleagues¹⁴ investigated somatosensory evoked magnetic fields in string players. Source analysis revealed that the cortical representation of the digits of the left hand (the fingering hand) was larger in these musicians than in controls. In the case of the right hand, in which no independent movements of the fingers are required in string players, there were no differences between musicians and controls. The cortical reorganization of the representation of the fingers was more pronounced in musicians who had begun their musical training at an early age. A first indication that extensive musical training can plastically alter receptive functions was provided by Pantev and colleagues¹⁵. Equivalent current dipoles, computed from evoked magnetic fields, were obtained in response to piano tones and to pure tones of equal fundamental frequency and loudness. In musicians, the responses to piano tones (but not to pure tones) were ~25% larger than in non-musicians. In a study of violinists and trumpeters, this effect was most pronounced for tones from each musician's own type of instrument¹⁶.

Although musical sounds were used in these early studies, they lacked a main characteristic of music: tones become music only when they are structured. The temporal structure of music comprises local rhythm, defined by the duration and temporal distance of tones, and global metrum, which determines whether a piece is, for example, a march or a waltz. As far as the pitch dimension is concerned, the interval between two successive notes, the global contour of a musical piece and the harmonic structure can be distinguished. In processing (and enjoying) music, the extraction of structural regularities is of paramount importance. At what cognitive and neural levels are such regularities of music processed? The mismatch negativity (MMN), a frontal negative wave in the event-related potential (ERP), is a marker of the pre-attentive detection of changes in regular sequences of auditory stimuli¹⁷. Consider, for

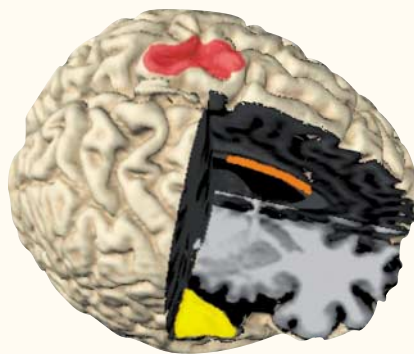


Figure 2 | Structural changes in the brains of musicians. Some of the brain areas that have been found to be enlarged in musicians in morphometric studies based on structural magnetic resonance imaging. Red, primary motor cortex; yellow, planum temporale; orange, anterior part of the corpus callosum.

example, a series of 1,200-Hz tones that is interrupted occasionally by a deviant 1,500-Hz tone. In this situation, the deviant tones give rise to an MMN. Importantly, the MMN occurs in the absence of attention to the stimuli, and newer research has indicated that, in addition to simple physical deviants (such as duration, pitch or intensity), the MMN is also elicited by more complex irregularities, such as changes in sequences of several tones¹⁷.

Professional musicians, unlike non-musicians, show an MMN for tones that are mistimed by as little as 20 ms in a series of regularly spaced tones¹⁸. For stimuli that are mistimed by 50 ms, which do produce an MMN in non-musicians, the MMN in musicians was considerably larger than that of controls¹⁸. Musicians also showed an MMN for slightly impure chords that were presented among perfect major chords, whereas, again, non-musicians did not¹⁹. Recently, an MMN was found for small changes in the contour of transposed melodies in musicians who perform primarily without a score²⁰. Source localization studies have shown that the MMN arises mainly from neurons on the supra-temporal plain of the temporal lobe, with further contributions from the frontal cortex^{17,21,22}. These findings indicate that, after years of musical training, neuronal populations in the auditory cortex might be shaped such that they automatically detect subtle changes in auditory stimulus sequences with simple or higher-order regularities. The parameters that are needed for the acquisition of these skills are unknown, but probably involve initial attentive processing of the stimuli²⁰.

In an experiment that required the attentive analysis of chord sequences, the N1 component of the ERP, which arises from the primary auditory cortex, was enhanced in

response to consonant chords, relative to dissonant (augmented fifth) chords, in musicians only²³. This indicates that the auditory cortex, possibly including the primary areas, in musicians might be tuned to complex harmonic features of sounds²⁴. Superior attention-dependent processing in musicians was also shown in a study that required the subjects to select stimuli from one of two information channels that were defined by their pitch. In such situations, stimuli that are attended elicit a negativity in the event-related potential, known as the Nd, relative to stimuli that are not the focus of attention²⁵. In professional musicians, the Nd was more pronounced, indicating superior attentional selectivity in the pitch dimension²⁶.

A recurring theme in the animal literature is the plasticity of sound localization. Inter-aural differences in the level and phase of sounds are important for sound localization, but the filter functions of the outer ear, known as head-related transfer functions²⁷, also provide crucial information. A conductor, more than any other musician, is likely to depend on spatial localization for successful performance — for example, he might need to home in on a certain player. Consistent with this, professional conductors were found to be better than pianists and non-musicians at separating adjacent sound sources, one of which was task relevant, in the periphery of the auditory field. This behavioural selectivity was paralleled by modulation of the Nd component, which was selective for the attended source in conductors, but not in pianists or non-musicians²⁸.

Anatomical differences

Since the age of phrenology, neuroscientists have tried to relate extraordinary skills to changes in brain anatomy. For example, at the beginning of the twentieth century, Auerbach reported that the middle and posterior thirds of the superior temporal gyrus were larger than normal in several post-mortem studies of the brains of famous musicians²⁹. Modern brain-imaging techniques, such as high-resolution magnetic resonance imaging (MRI), allow us to study anatomical details in the brains of living humans. Studies in which these techniques have been used have shown that several brain areas, including the planum temporale, the anterior corpus callosum, the primary hand motor area and the cerebellum, differ in their structure and size between musicians and control subjects (FIG. 2). These findings have reopened the debate about whether these structural differences are related directly to musical ability.

Asymmetry of the planum temporale has been suggested as a marker of cerebral dominance, because its direction and size correlate with handedness³⁰. In two independent samples, musicians with absolute pitch (AP) had a more pronounced leftward planum temporale asymmetry than did musicians with relative pitch (RP) or non-musician controls^{31,32}; another study found no significant difference in planum temporale volume between musicians with AP and those with RP³³. However, when compared with a large sample of right-handed non-musician controls, musicians with AP again showed a larger left planum temporale (BOX 1).

Amunts and colleagues³⁴ have estimated the size of the primary hand motor area by determining the intrasulcal length of the posterior bank of the precentral gyrus in linearly normalized MRI images. Musicians had a greater intrasulcal length on both sides, but more so on the right, non-dominant hemisphere, resulting in reduced asymmetry scores for this area in musicians. There was a strong negative correlation between the time at which musical training had begun and the size of the right- and left-hand motor areas. This was reflected behaviourally by reduced asymmetry in measurements of hand skill and a negative correlation between hand-skill asymmetry and the age at which musical training started³⁵.

Many musical instruments require precise coordination of bimanual movements. Interestingly, musicians who began their musical training before the age of seven have a larger anterior midsagittal corpus callosum than controls or musicians who started training later³⁶. Because the size of the midsagittal corpus callosum is a good indicator of the number of axons that cross the midline³⁷, this finding indicates that this subgroup of musicians has an enhanced interaction between the two hemispheres. This hypothesis has been corroborated by a bilateral transcranial magnetic stimulation (TMS) study in pianists and guitarists³⁸, which revealed decreased interhemispheric inhibition. This, in turn, might facilitate bimanual coordination in musicians by increasing signal transfer between the hemispheres.

The precise timing of movements also requires the participation of the cerebellum. Recently, male musicians have been shown to have a greater mean relative cerebellar volume than male non-musicians. The difference could not be ascribed to a difference in total brain volume, as this was similar in both groups³⁹. Together, the findings indicate that musicians have anatomical differences in several brain areas that are involved in

motor and auditory processing. Changes in such large-scale neural networks can be detected by voxel-based morphometry⁴⁰, a statistical method of revealing differences in brain anatomy, viewed by MRI, between groups, without the need to focus on target structures. Such an analysis revealed increased grey matter volume in musicians in a motor network that included the left and right primary sensorimotor regions, the left basal ganglia, and the bilateral cerebellum, as well as the left posterior perisylvian region⁴¹.

Sensorimotor learning

It has been proposed, on the basis of neuroimaging studies, that motor learning occurs in several phases: a fast initial phase of performance gains is followed by a period of consolidation that lasts for several hours. This is succeeded by a slow learning phase that occurs during continued practice and leads to gradual increases in performance⁴². With regard to slow learning, practising a complex tapping task over several months led to an increase in functional MRI (fMRI) activation in the primary motor area by ~25% in non-musicians⁴³. When highly skilled pianists and non-musicians were exposed to a novel tapping task during a single scanning session, musicians showed a rapid increase in M1 (primary motor cortex) activation, whereas non-musicians did not⁴⁴. This effect

of recruitment in the primary motor area of musicians resembled the slow learning described previously in non-musicians⁴², even though it occurred within minutes rather than months. It was therefore interpreted as an effect of pre-practice experience⁴⁴. With regard to secondary motor areas, musicians showed a much smaller area of activation in the supplementary motor area (SMA), pre-SMA and cingulate motor area than non-musicians in several studies^{44–46}. So, pianists recruit smaller neural networks than do non-musicians, indicating that they are more efficient in the control of movements.

In musically naive subjects, training on the piano for two hours per day over five days led to increased excitability of the cortical motor areas that control the contralateral finger flexor and extensor muscles of the hand⁴⁷, as measured by mapping of the responses to TMS. A similar but less pronounced effect was observed in subjects who mentally rehearsed the motor tasks over five days. Mental practice therefore seems to be sufficient to promote the modulation of neural circuits that are involved in the early stages of motor-skill learning⁴⁷.

Exceptional musical performance requires the high-speed control of complex movement patterns under continuous auditory feedback. As a prerequisite, audio-motor integration at cortical and probably subcortical levels has to be established. This audio-motor coupling —

Box 1 | Absolute pitch

Perfect or absolute pitch (AP) is defined as the ability to identify accurately the pitch of a single tone heard in isolation, usually in terms of musical-scale categories or keys on a piano. Estimates of the prevalence of AP vary widely from 1 in 1,500 in amateur musicians⁶² to up to 15% in students at music schools⁶³. Although AP was initially considered to be an innate ability⁶⁴, there is now a consensus that it relies on both a genetic predisposition^{65,66}, possibly even a major gene effect, and early musical training^{32,63}. Anatomically, an *in vivo* magnetic resonance imaging (MRI) morphometric study of musicians has shown increased left-sided asymmetry of the superior bank of the temporal lobe, the planum temporale (PT)³¹, in individuals with AP. Interestingly, this asymmetry seemed to be the result of a smaller-than-normal right PT in musicians with AP, rather than an expansion of the left side³². Attempts to correlate anatomical measures with performance in pitch-identification tasks have yielded conflicting results, with the size of either the right³² or the left³³ PT being the better predictor of performance in musicians with AP. However, a recent functional MRI study found that the intensity of haemodynamic responses to music pieces in the left, rather than right, PT correlates with both AP ability and the age at which musical training started⁶⁷. Early training alone cannot account for the PT asymmetry, as musicians with relative pitch (RP) who started training early do not have such an asymmetry³². In functional terms, it has been suggested on the grounds of a smaller⁶⁸ or even absent⁶⁹ P300 event-related potential — generally interpreted as an index of working memory updating — that musicians with AP do not rely on auditory working memory for pitch identification. This view is supported by a positron emission tomography study that revealed stronger activation of a right inferior frontal area, which is proposed to be involved in tonal working memory, in musicians with RP carrying out a task that required an interval judgement for two successive tones. On the other hand, musicians with AP, but not RP, showed activation in the posterior left dorsolateral frontal region, which is thought to support verbal–tonal associations, in a passive listening task³³.

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which is comparable to the oral–aural loop in language processing — is established during musical training⁴⁸. At the behavioural level, it is reflected by reports from professional pianists that their fingers move more-or-less automatically when they are listening to piano music. Exposing musically naive subjects to controlled piano training led to audio-motor coupling after as little as 20 minutes of training, as shown by topographic analysis of very slow event-related potentials⁴⁸. After the first training session, there was further activity over motor areas while subjects listened to simple piano tunes. Likewise, finger movements on a mute keyboard were associated with an increase in activity over auditory areas. The effect could be enhanced and stabilized during five weeks of training (FIG. 3). Similar co-activation has also been found in professional pianists, who showed magnetoencephalographic (MEG) activity in sensorimotor

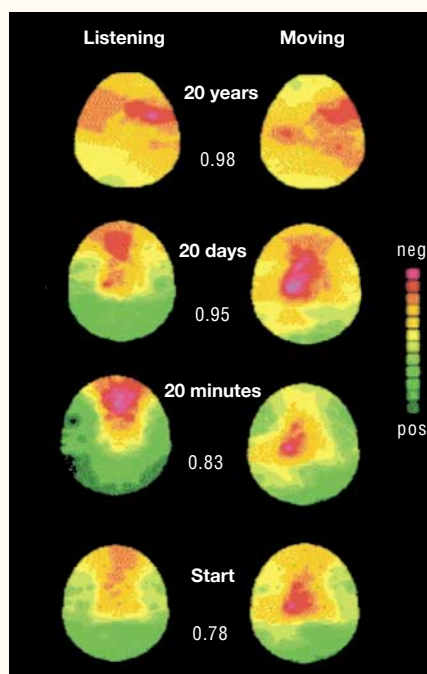


Figure 3 | Sensorimotor integration in musicians. Shown are spline-interpolated isovoltage maps of averaged electroencephalographic recordings. Subjects either listened to a short piece of piano music (left column) or performed on a mute piano keyboard (right column). Before training, musically naive subjects (Start) produced grossly different topographic patterns of slow event-related potentials in the two conditions, as indicated by the maps and a measure of map similarity (scalar product). With training for 20 minutes or 20 days, the topographic distributions became increasingly similar. In professional pianists with approximately 20 years of training, maps in both conditions are virtually identical. Modified, with permission, from REF. 48 © 2001 New York Academy of Sciences.

cortical regions while listening to piano music⁴⁹. These neural networks thus seem to behave in a similar way to the 'mirror neurons' in the monkey frontal cortex (area F5), which are active during both the execution of complex movements and visual observation of the same movements⁵⁰.

Maladaptive plasticity

There is a dark side to the increasing specialization and prolonged training of modern musicians — namely, loss of control and degradation of skilled hand movements, a disorder referred to as 'musicians' cramp' or focal dystonia¹². The first historical record of this condition, from 1830, appears in the diaries of the famous pianist and composer Robert Schumann⁵¹. As was probably the case for Schumann, prolonged practice and pain syndromes due to overuse can precipitate dystonia, which is developed by ~1% of professional musicians and usually ends their careers¹². Neuroimaging studies point to dysfunctional (or maladaptive) neuroplasticity as its cause^{13,52}. For example, an MEG study of musicians with focal dystonia showed fusion of the digital representations in the somatosensory cortex, reflected in a decreased distance between the representations of the index and little fingers relative to healthy control musicians¹³ (FIG. 4). These findings are corroborated by psychophysical measurements and fMRI investigations in a related disorder, writer's cramp, which showed decreased temporal and spatial discrimination at the finger tips^{53,54}. Observations in monkeys indicate that rapid, stereotypical movements in a learning context can actively degrade the cortical representations of sensory information that guide fine hand movements⁵⁵. This dedifferentiation of sensory feedback information has been proposed to form the basis of focal dystonia^{47,55}. Indeed, the repeated temporal association of movement patterns is a characteristic of music — for example, when playing arpeggios or musical scales. In a further study, symptoms were provoked in five dystonic guitarists when they played a modified guitar inside an fMRI scanner⁵⁶. Relative to non-dystonic guitarists, they showed more activation of the contralateral sensorimotor cortex but less activation of premotor areas, indicating abnormal recruitment of cortical areas that are involved in the control of complex movements.

Musicians as a model?

Neuroplasticity allows the brain to adapt to environmental factors that cannot be anticipated by genetic programming. The neural and behavioural changes that are attributed

to plasticity have been observed on different timescales, ranging from several minutes to the whole lifetime of the individual. Different processes are likely to support plastic changes at the extremes of this timeline. Accordingly, experience-driven neuroplasticity has been explained by both the *de novo* growth and improvement of new dendrites, synapses and neurons^{5,57}, and the disinhibition or inhibition of pre-existing lateral connections between neurons by sensory input⁵⁸. The former mechanism entails structural changes at the microscopic and macroscopic levels, whereas the latter can be achieved by strengthening or inhibiting pre-existing synaptic connections in the spirit of Hebbian learning. Sometimes, even more rapid changes of brain responses, occurring in the order of milliseconds, have been discussed under the heading of neuroplasticity. However, these are likely to result from the attentional modulation of neural circuits, and should be distinguished from true plastic changes⁵⁹.

Research into plasticity in musicians is still in its infancy, but, already, many of the findings from animal studies have found parallels in studies of musicians. At one extreme, years of musical experience, especially in those musicians who begin training early on, might lead to an increase in grey and white matter volume in several brain regions^{31,32,36,39,41}. These anatomical alterations seem to be confined to a critical period. The fact that, in several studies, a correlation was found between the extent of the anatomical differences and the age at which musical training started strongly argues against the possibility that these differences are pre-existing and the cause, rather than the result, of practising music. The view that these differences represent genuine plastic changes of the brain receives further support from neuroimaging studies in other populations. For example, a correlation between the size of the posterior hippocampus and years of driving experience has been reported in London taxi drivers⁶⁰. Further research using advanced imaging techniques, such as magnetic resonance spectroscopy and diffusion tensor imaging, and the extension of studies beyond the conventional cross-sectional design, are needed to investigate the underlying neurophysiological changes.

At the other extreme, several minutes of training can induce changes in the recruitment of areas of the motor cortex⁴⁴ or establish auditory–sensorimotor coupling⁴⁸. Some of the other findings discussed here probably require training in the order of months to several years and, at present, it is unclear what neural processes support this behavioural plasticity.

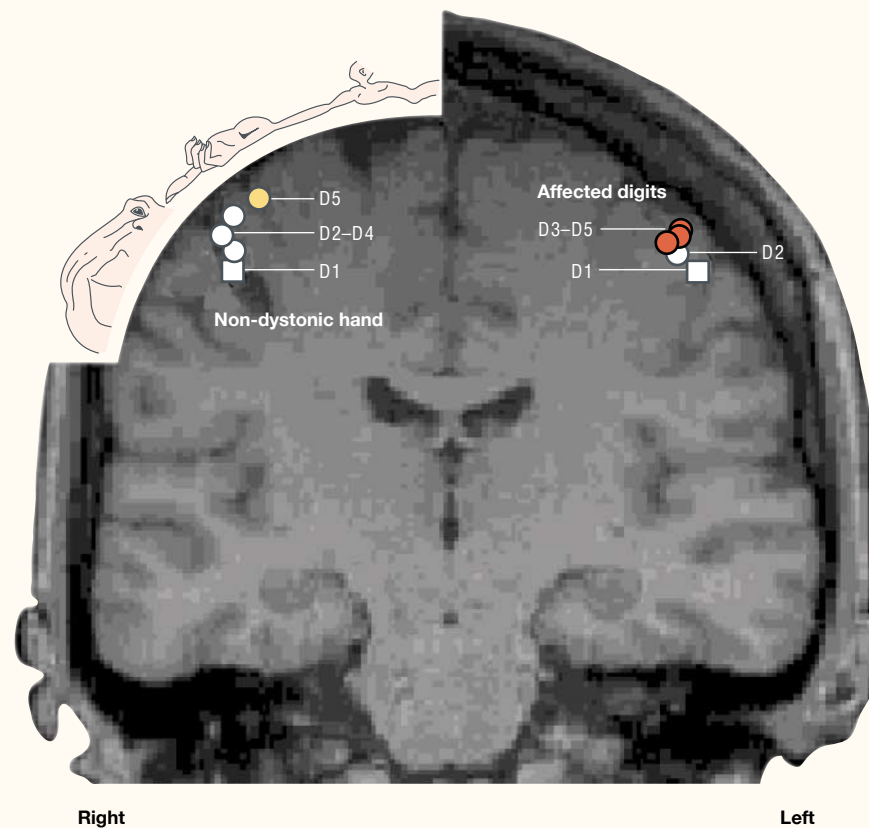


Figure 4 | Fusion of the somatosensory representation of single digits of the hand in a musician suffering from focal dystonia. The best-fitting dipoles to explain the evoked magnetic fields after sensory stimulation of single digits (D1–D5) are shown projected on the individual's magnetic resonance imaging scan. Whereas for the non-affected hand, the typical homuncular organization (inset) reveals a distance of ~2.5 cm between the sources for the thumb and the little finger (yellow circle and square on the right of the brain), the somatosensory representations of the fingers on the dystonic side are blurred, resulting from a fusion of the neural networks that process incoming sensory stimuli from different fingers (red circles). Modified, with permission, from REF. 13 © 1998 Lippincott, Williams and Wilkins.

The investigations presented in this overview convincingly show the value of the musician's brain as a model of neuroplasticity and have set the stage for further research. Some of the questions that need to be tackled include the following. What are the training parameters that lead to successful learning and plasticity? Can these parameters be exploited in musical education or to enhance learning in other domains? What is the role of genes in determining auditory neuroplasticity in musicians? What is the range of structural regularities that can be extracted from the auditory input in an automatic, pre-attentive fashion? As making music undoubtedly requires intense self-monitoring, and error detection and correction, are there any plastic changes in the executive brain systems that are responsible for performance monitoring?

Finally, one has to bear in mind that music can elicit powerful emotional reactions. Strong emotional responses to music, leading

to shivers down the spine and changes in heart rate, are accompanied by the activation of a brain network that includes the ventral striatum, midbrain, amygdala, orbitofrontal cortex and ventral medial prefrontal cortex — areas that are thought to be involved in reward, emotion and motivation⁶¹. Further research will show whether activity in these areas is also directly involved in mediating neuroplasticity.

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OPINION

Complex-trait genetics: emergence of multivariate strategies

Tamara J. Phillips and John K. Belknap

Complex traits, including many disease-related traits, are influenced by multiple genes. Bivariate approaches that associate one gene with one trait are yielding to multivariate methods to synthesize the effects of multiple genes, integrate results across independent studies, and aid in the identification of coordinated pathways and interactions between loci.

The extraordinary success of the molecular revolution in transforming modern biology has generated one important problem — how do we synthesize the wealth of molecular data to gain insight into ‘higher-order’ processes that exist at the levels of pathways, organ systems and whole organisms? This question has led to the rise of newer, synthetic research strategies to complement those based on dissection and analysis. This trend is evident in the genetic analysis of complex central nervous system traits — the subject of this article.

Complex (or quantitative) traits are those influenced by multiple loci (genes), each of which is known as a QUANTITATIVE TRAIT LOCUS (QTL). Approaches to the study of complex traits are of two general kinds, each with

strengths and weaknesses¹. Gene-driven methods focus on a particular gene and seek to determine the phenotypes that are influenced by that gene. The study of knockout animals is a prime example. By contrast, trait-driven methods focus on a specific trait (phenotype) and seek to discover the underlying genes. QTL mapping, genome-wide mutagenesis screens and MICROARRAY expression analysis are examples of this approach. Because of their ability to focus simultaneously on many genes, trait-driven methods lend themselves more readily to multivariate genetic approaches than do gene-driven methods. However, some examples of the latter are also amenable to multivariate approaches (such as the use of double knockouts), as we discuss below.

Arguably, the first important advances in the study of complex-trait genetics were made by gene-driven knockout and transgenic strategies, which have been used to identify hundreds of genes that probably influence specific complex traits. Much of the progress that has been made so far has been based on bivariate approaches — one locus is shown to influence one trait, or a series of bivariate experiments are used to link one locus to