

NEURAL SUBSTRATES OF MOVEMENT AND MUSIC: AN FMRI APPROACH

by

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The Charles E. Schmidt College of Science
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by

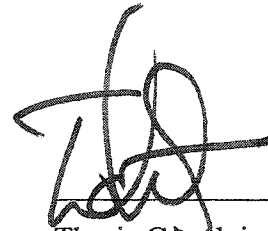
Dinesh G. Nair

This dissertation was prepared under the direction of the candidate's thesis advisors, Dr. J.A. Scott Kelso and Dr. Edward W. Large, Center for Complex Systems and Brain Sciences, and has been approved by the members of his supervisory committee. It was submitted to the faculty of The Charles E. Schmidt College of Science and was accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

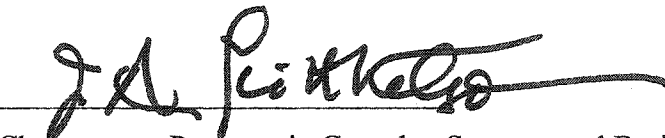
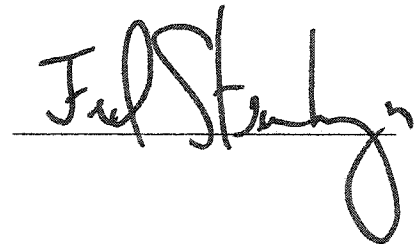
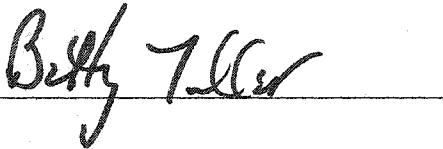
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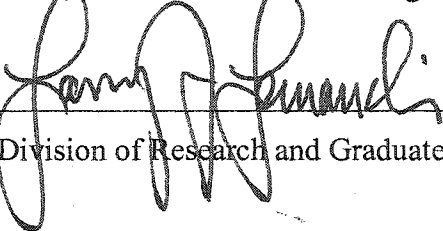
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Abstract

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In this dissertation, we examined the neural correlates of motor coordination and music perception using a set of four fMRI experiments. The neural correlates of goal-directed action were examined in a group of healthy adults in experiment 1 using execution and imagery of a unimanual and a bimanual finger-sequencing task. Similar neural networks were engaged for execution and imagination of movement sequences. Interestingly, we also found that the sensorimotor cortical and cerebellar areas are functionally decoupled from the task network when people imagine but do not actually execute sequential actions.

In experiment 2, we used the same finger-sequencing paradigm to study recovery of function during recovery from stroke. It was observed that the wide spread neural activity during the initial session became more localized during the last session. In addition, using imagery tasks, we showed that hemiplegic patients retained the ability to activate neural pathways that are normally involved in executing goal-directed action sequences, despite the loss of ability to actually execute movements.

In experiment 3, we examined brain activity when musicians and non-musicians listened to expressive and mechanical versions of a musical piece. The expressive performance activated the limbic areas more than the mechanical version in both groups of subjects suggesting perception of affect. The pattern of neural activity was also dictated by their experience and familiarity with the piece of music. In addition, we found activation of language related areas when musicians listened to the expressive version suggesting shared neural resources for language and music.

The neural basis of sensorimotor coordination and timing in Parkinson's disease was investigated in the last experiment, using a synchronization-syncopation task and the continuation paradigm. Different neural areas subserved timing during the two different modes of coordination. However, these differences persisted during their respective continuation phases. In order to compensate for the functional deficiency in Parkinson's disease, patients recruited functionally segregated circuits that connect the striatum and association areas of the parietal, premotor and prefrontal cortices.

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Superior Temporal Gyrus; IFG – Inferior Frontal Gyrus; MFG – Middle Frontal Gyrus; PCC – Posterior Cingulate Cortex; VLN – Ventral Lateral Nucleus; MDN – Medial Dorsal Nucleus of thalamus; Pulv – Pulvinar; SFG – Superior Frontal Gyrus; SMG – Supramarginal gyrus; SMC – Sensorimotor Cortex; IPL – Inferior Parietal Lobe; SPL – Superior Parietal Lobe; SMA – Supplementary Motor Area.

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Chapter 1

Introduction

Cognitive neuroscience focuses on elucidating the biological underpinnings of mental processes and seeks to unravel the mysteries of the human brain. Researchers over the past decade have combined experimental strategies in Psychology with techniques that allow them to examine how brain activity supports mental processes. Foremost among these techniques is functional Magnetic Resonance Imaging (fMRI). The most common method of fMRI is blood oxygenation level dependent (BOLD) imaging, in which hemoglobin is used as an endogenous contrast agent. This method relies on the difference in magnetic properties of oxyhemoglobin (diamagnetic) and deoxyhemoglobin (paramagnetic) (Ogawa et al., 1990) and hence provides a non-invasive tool to look into the human brain when a person performs motor, sensory or cognitive tasks. This dissertation is comprised of four fMRI experiments, aimed at identifying neural activation during different motor coordination tasks and music perception. Motor coordination was studied not only in the healthy adult individuals but also in stroke and Parkinson's disease.

1.1 Motivation

Music and movement are so intimately related to each other that tapping our foot while listening to music, clapping rhythmically and dancing to music occur quite naturally to most of us. The relation between music and behavior extends beyond rhythmic tapping and several interesting phenomena have been observed with music,

the mechanisms of which are yet to be understood. Music and rhythmic auditory stimuli reduce rigidity and tremor in Parkinson patients and improve motor control (Thaut et al., 1996; McIntosh et al., 1997; Johnson et al., 1998). Oliver Sacks in his book "Awakenings", reports that patients with neurological disorders who cannot talk or move are often able to sing, and sometimes even dance, to music. Music even induces positive behavioral changes in patients with psychiatric disorders, helps patients in intensive care units achieve faster recovery, reduces anxiety, enhances sleep and decreases distraction, agitation and depression (Clarke et al., 1998; Chlan and Tracy 1999; Tjellesen et al., 2001). We have personally observed that people who stammer when they speak, rarely do so when they sing. These remarkable phenomena point to the ability of music and rhythmic stimuli to influence not just motor behavior but the overall emotional well being of individuals. How does listening to music become an aesthetic experience? What happens in the human brain when we enjoy music? How does listening to rhythmic stimuli and music modulate motor behavior? How are rhythmicity and motor timing related? Are there separate neural representations for different timing requirements? What are the neural underpinnings of these phenomena? These questions have motivated the research described in this dissertation. The key to unlocking the basis of some of the interesting observations mentioned above lies not only in identifying brain areas involved in music perception and motor control, but in understanding their functional connectivity as well.

The use of fMRI to study task-induced brain activation during goal-directed behavior extends across several domains of research including motor, sensory and various

facets of cognition (language, memory, emotions and reasoning to name a few). In most studies researchers ask subjects to engage in some task while scanning their brain and interpret their brain activity post-hoc. However, in the sea of fMRI studies published over the last decade, the importance of a proper scientific interpretation of the BOLD response has been underplayed in several ways. First, an often forgotten but important issue regarding interpretation of functional MRI signals is that the functional brain maps that we see are static representations of this dynamic activity averaged over a long period of time. This is especially true in the case of block designs. Second, in the literature we see an unhealthy trend of attributing functional significance to brain areas piecewise. If one knows the processes implemented in a particular brain area for sure, one can argue that activation of this area in response to a task, is evidence that these processes were employed while performing the task. But there may not exist a one to one relationship between a task and a brain region, even for specific areas of the cortex such as primary motor cortex. More and more evidence points to the brain as a highly interconnected, spatiotemporal dynamic system that uses distributed representational schemes (Kelso, 1995; Haken, 1996; Friston, 2000). Hence it is likely that for every task, there are brain areas unique to the task as well as neural resources shared by different task components. Third, localizing neural activity alone does not give us a better understanding of the neural processes involved in the task (Kosslyn, 1999).

A carefully designed experiment is the first step in avoiding many problems mentioned above. Researchers if possible, should first have a set of questions or

hypotheses that they would like to test. Then comes designing a task to test the hypothesis. The experimental protocol, including the scanning method and the spatiotemporal resolution of the signal is decided by the nature of the task and the questions addressed in the experiment. Since subtraction of activity is the most widely used method to identify brain areas active in one condition relative to another, the task pairs should ideally differ in only one parameter. However, this assumes that changing one parameter of the task alters only one aspect of processing! As described further along this chapter, this is very unlikely given the plethora of ongoing neural activity even at the resting state. In the following chapters we try to interpret brain activity with the above considerations in mind, relating activation to the cognitive demands of the task and also with the known functional connectivities of these brain regions. In this process we also take into consideration the plasticity of the brain and how alternate brain regions and neural pathways adapt to the requirements of the task, when the primary network is functionally deficient due to some disease process.

1.2 Organization of this dissertation

We designed four experiments using fMRI to study motor coordination in both healthy subjects and patients with stroke and Parkinson's disease, and music perception in normal adult volunteers. Chapter 2 describes a study that examined fine motor coordination in adult right-handed individuals using a finger-sequencing task with varying levels of cognitive demands. This task consisted of execution and imagery of unimanual and bimanual finger sequences. We found evidence for engagement and disengagement of several cortical and sub-cortical areas into the

motor network to perform this task. Interestingly, imagery of the task utilized similar neural resources as overt execution. This finding motivated us to use the same task to examine functional recovery in a stroke patient. The essential idea was that if hemiplegic patients retain the ability to represent movements even when not being able to actually execute them, then motor imagery provides a means of stimulating the damaged neural networks despite difficulties in limb movements. We scanned a stroke patient on three occasions using the same task, to see how brain activity changed over time as he recovered. This study is described in chapter 3. Although previous studies have provided evidence for a beneficial effect of music and rhythm on motor coordination in health and disease, it is unclear whether it is the rhythmic nature of the musical stimulus per se or the motivational aspects of music, that modulated this auditory-motor loop. Chapter 4 describes an fMRI experiment designed to study music perception in general and to investigate whether expressive cues in music performance lead to limbic activity. A group of professional musicians and non-musicians were scanned in order to delineate the effects of training on perception. Since timing is an integral part of rhythm and motor coordination, in a fourth study (chapter 5) we examined a group of Parkinson's disease patients who are in general known to be deficient in perception and production of temporal intervals. Employing two modes of coordination with different timing demands, we explored the neural correlates of timing and coordination in Parkinson's disease patients and age-matched control subjects. Results revealed how different regions in the brain organize themselves and modify functional connectivity to compensate for the loss of function. We conclude with chapter six which summarizes our findings from these

studies. In order to interpret fMRI signals in a prudent manner, it is imperative that one knows what exactly the BOLD signal represents. The rest of this chapter provides an overview of some recent work on the neural basis of BOLD fMRI.

1.3 BOLD fMRI

BOLD fMRI measures a correlate of neural activity, the hemodynamic response. The hemodynamic response, as the name implies is dynamic, and depends on cerebral oxygenation, blood flow and blood volume (for reviews see Menon & Kim, 1999; Heeger et al., 2000; Arthurs & Boniface, 2002; Heeger & Ress, 2002; Attwell & Iadecola, 2002; Ugurbil et al., 2003). An accurate interpretation of the BOLD signal depends on how effectively one characterizes the nature of the underlying neural activity that gives rise to the hemodynamic response and how these two (neural activity and blood flow response) are coupled. IN order to do so, we need a better understanding of what happens in the brain at the level of neurons and their immediate microvasculature and also about other factors that modulate the BOLD signal.

1.3.1 At the synapse

Continuous neural activity and maintenance of homeostasis are dependent on active processes requiring energy such as restoration of ionic gradients and repacking of neurotransmitter molecules. Under normal resting conditions, the brain's energy demands are met (ATP production) almost exclusively by glucose oxidation. More than 90% of resting state glucose consumption is oxidative. Since the energy yield of

glucose oxidation is much more than that of glycolysis (at least 15 times more ATP), more than 99% of the ATP production in the resting stage is by glucose oxidation (Fox et al., 1988), oxidizing glucose to water and CO₂. Fox et al. (1988) reported that the mean whole brain cerebral metabolic rate for oxygen (CMRO₂) and that for glucose (CMRGlu) are in a 4.1:1 molar ratio during the resting state. This increased cerebral metabolic rate for O₂ verifies the finding of greater glucose oxidation and hence oxidative mechanisms for ATP production during rest. Functional activation increases cerebral metabolic rate for glucose and cerebral blood flow by about 50%. However, cerebral metabolic rate for O₂ increased only by 5% (Fox & Raichle, 1986; Fox et al., 1988). Thus about 90% of the activity-induced increase in glucose uptake is not oxidized. The non-oxidative, alternative pathway for glucose metabolism is glycolysis which results in an increase in lactate production. Moreover, with an increase in cerebral blood flow that far exceeds cerebral metabolic rate for O₂, a highly significant reduction in oxygen extraction fraction occurs. Creutzfeldt (1975) estimated that only a maximum of 3% cortical energy consumption was accounted for by spike activity of cortical nerve cells. Hence even if neural activity doubled, cerebral metabolic rate for O₂ did not increase beyond 6%. This agrees with the percentage rise in BOLD signal that is typically seen during functional activation in fMRI studies.

Astrocytes are stellate cells that have processes around the synapse and also around intraparenchymal capillaries (end feet). The enormous number of astrocytes in the brain (astrocyte:neuron = 10:1) and their anatomical proximity to the synapse and capillaries make them ideal candidates for coupling neuronal activity with

metabolism (Magistretti & Pellerin, 1999; Magistretti & Pellerin, 2000). It has been shown that a glucose transporter (GLUT1 type), is expressed on astrocytic end feet (Morgello et al., 1995) and the synaptic contacts (of astrocytes) possess receptors for various neurotransmitters, especially glutamate. Activated synaptic terminals release glutamate, which acts on target neurons mediated by glutamate receptors. This action is terminated by a reuptake system, present in the astrocytes. How astrocytes couple this glutamate reuptake system with glucose uptake from capillaries is the key to the metabolic processes that follow NT release into the synapse (fig 1.1). Removal of glutamate from the synaptic cleft takes place through specific glutamate receptors GLT-1 and GLAST, which are glial specific (Robinson & Dowd, 1997). Glutamate uptake is driven by the electrochemical gradient of sodium ions, three Na^+ being co-transported along with one glutamate into the astrocyte. Inside the astrocyte, glutamate is converted into glutamine, which is taken back into the neuron to replenish the glutamate reserve. Glutamate uptake into the astrocyte also stimulates glucose uptake into the astrocyte from the capillaries and glycolysis. This is mediated by Na-K-ATPase since ouabain, a Na-K-ATPase inhibitor completely inhibits the glutamate-evoked 2DG uptake by astrocytes (Pellerin & Magistretti, 1994). Activity-induced glycolysis results in an increase in lactate concentration (Prichard et al., 1991) inside astrocytes, which is further transported into neurons to meet the energy demands of active neurons. Lactate dehydrogenase (LDH), the enzyme that catalyzes the conversion of lactate to pyruvate has been found in neurons (specifically the LDH1 type, which is the form found in lactate-consuming tissues) (Bittar et al., 1996). This suggests that the lactate that enters neurons from astrocytes could be

converted to pyruvate, which enters the TCA cycle to serve as energy molecules (see fig 1.1). Atwell & Laughlin (2001) estimated the metabolic costs of brain activity and showed that most of the energy is used by neurons depending on their firing rate; only a small percentage of energy is used for neurotransmitter recycling by astrocytes.

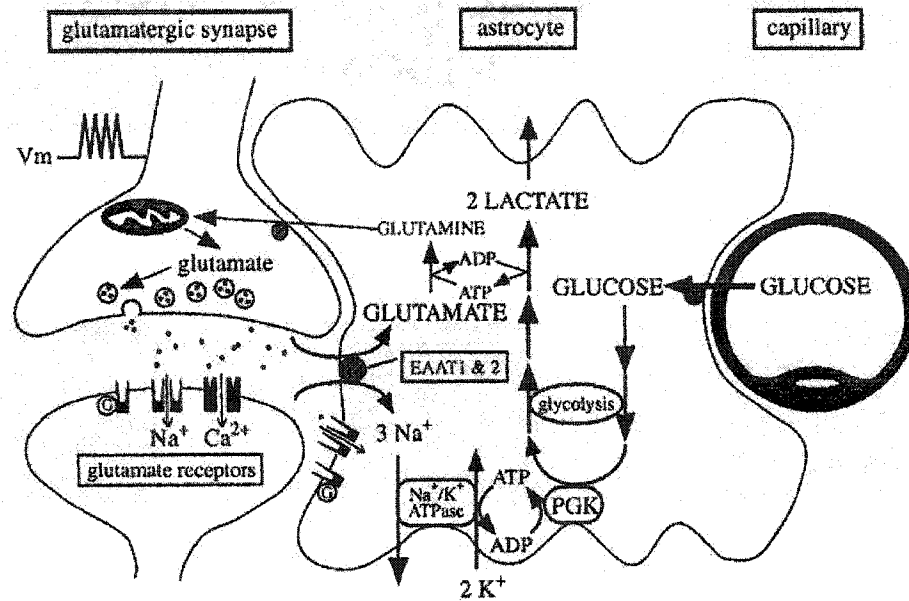


Fig.1.1. Schematic representation of the mechanism for glutamate-induced glycolysis in astrocytes during physiological activation. Pre-synaptically released glutamate depolarizes post-synaptic neurons by acting at specific receptor subtypes. The action of glutamate is terminated by an uptake system located primarily in the astrocytes. Glutamate is co-transported with Na^+ , resulting in an increase in the intra-astrocytic concentration of Na^+ , leading to the activation of Na^+/K^+ -ATPase. Activation of this enzyme stimulates glycolysis – i.e. glucose use and lactate production. Lactate once released by astrocytes are taken up by neurons and serves as an adequate energy substrate. Adapted from Magistretti and Pellerin, 1999.

The mechanisms of neural activity-induced increase in blood flow and metabolism can be summarized as follows.

- i) Neural activity is followed by a relatively large increase in blood flow and cerebral metabolic rate for glucose with a slight increase in cerebral metabolic rate for O₂.
- ii) Glutamate release induces glucose transport into astrocytes aided by Na⁺-K⁺ATPase activity.
- iii) Astrocytes rely on non-oxidative glycolysis as suggested by the increase in lactate levels. Neurons depend on oxidative metabolism of lactate.

In addition to glutamate, there are other signals in the brain that stimulate an increase in blood flow. These include metabolites such as lactate, K⁺, H⁺ or adenosine, nitric oxide (NO) and neurotransmitters such as vasoactive intestinal peptide (VIP), acetylcholine (ACh) and noradrenaline (for details see Kuschinsky, 2000; Magistretti & Pellerin, 1999).

The issue of activity-dependent glycolytic processing of glucose is currently under debate. Using ¹³C-Glucose magnetic resonance spectroscopy, Hyder et al. (1996) reported data that supports an increase in oxygen use during neural activation. Based on Magistretti and Pellerin's model it is possible that an initial glycolytic processing of glucose in astrocytes is followed by oxidation of lactate in neurons. But how much oxygen is used is not known. Thompson et al. (2003) studied the relation between single neuron activity and tissue oxygenation in cat's visual cortex. They

simultaneously measured tissue oxygenation (using an oxygen microelectrode) and single-cell neural activity (using an adjacent platinum microelectrode) and found that increases in neuronal spike rate were accompanied by immediate decreases in tissue oxygenation. This initial decrease in oxygenation is believed to be responsible for what has come to be known as the “initial dip” in the BOLD response. Thompson et al. (2003) found that like hemodynamic responses, the time course of the oxygen response exhibited the initial dip followed by a positive peak. Under optimal orientation conditions of the visual stimulus, large neural responses (spikes) occurred which were accompanied by immediate decreases in oxygenation as revealed by the largest initial dip. This result highlights the initial coupling between neural activity and oxidative metabolism. Fig. 1.2 gives an illustration of the time course of the initial dip in oxygen response and the hemodynamic BOLD response following neural spikes. The Thompson study also used this decrease in tissue oxygenation to predict orientation selectivity and ocular dominance of neighboring neurons. Since the initial negative dip occurs earlier than the blood flow response, this also could be taken as an evidence for a dynamic uncoupling of oxygen metabolism and cerebral blood flow (Buxton, 2001).

1.3.2. The initial dip

The short uncoupling between oxidative metabolism and blood flow (Fox & Raichle 1986; Magistretti & Pellerin, 1999; Thompson et al., 2003), which is responsible for the initial dip was first reported by Grinvald and colleagues (Frostig et al., 1990; Malonek & Grinvald, 1996) using optical techniques to measure dynamic changes in

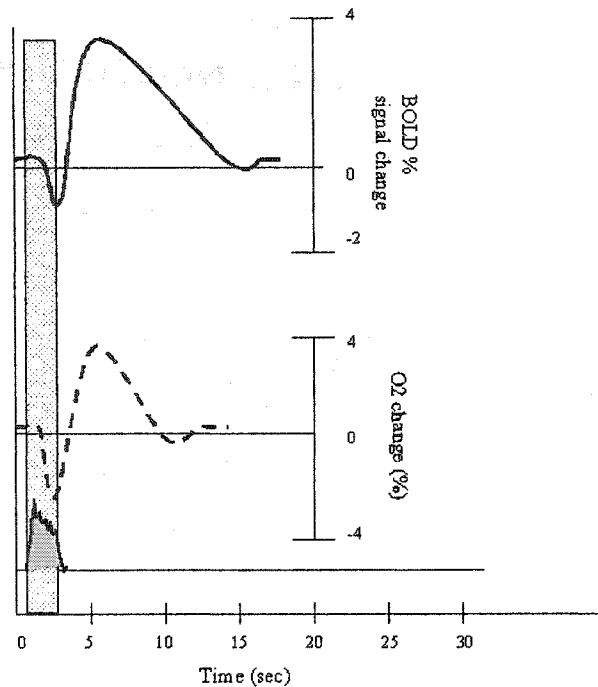


Fig. 1.2. Illustration of the temporal relationship of neuronal spikes, the oxygen curve and the BOLD response. The shaded vertical bar shows the duration of the stimulus. Neuronal spikes (gray solid area), oxygen curve (dotted line) and the BOLD response (top curve) are shown in the same time axis. The Y – axis for the BOLD and oxygen curves represent percentage change in signal. The initial increase in tissue oxygen extraction corresponds with the initial dip in the BOLD response. A delay (hemodynamic) of about 5 sec and a slow decay can also be seen for the BOLD response.

oxy- and deoxyHb in cats. The first human fMRI studies to demonstrate the initial response (Ernst & Hennig, 1994; Menon et al., 1995; Hu et al., 1997) used visual paradigms. These studies demonstrated that some focal areas of the visual cortex (columns that are highly selective to the visual stimulus) displayed an initial negative response while some others including those where draining veins are visible, showed only the positive signal change (Hu et al., 2000). Cortical columns responding specifically to the stimulus extract oxygen from the surrounding capillaries producing

an initial dip, while the ensuing hemodynamic response (increased CBF) compensates for this oxygen demand and hence one finds only the positive signal in areas adjacent to draining veins. The initial dip is highly controversial because not all studies show this early response. Jones et al. (2001) and Lindauer et al. (2001) used optical measurements in a rat model with stimulation of the whisker pad to look for the initial dip. Jones et al. were able to detect the dip while Lindauer et al. was not. Buxton (2001) wonders whether this could be due to the inherent variability of the physiological effect. It is possible that the initial dip is also very sensitive to imaging parameters. Among them, two are mentioned below. First, most imaging experiments that demonstrated the early response were conducted at high field strengths ($\sim 4\text{T}$). The relative amplitude of the early response scales more rapidly with field strength than the positive response (Hu et al., 2000). Second, Kim and his colleagues, in two studies with different end tidal CO_2 levels (Kim et al., 2000; Harel et al., 2002) found the initial dip only in the study with a larger end-tidal CO_2 . Larger end-tidal CO_2 presumably leads to more oxygen extraction immediately after neuronal firing and hence more deoxyhemoglobin, leading to a pronounced initial dip.

1.3.3. Neural firing / spikes

When a particular brain area is recruited in carrying out a task, a group of neurons in this area fire action potentials. However, there may be groups of neurons which do not fire action potentials, but nevertheless utilize oxygen - for instance, neurons at sub-threshold levels of activation, neurons with varying levels of simultaneous excitation and inhibition, and feedback from local and distant sites. In addition, the

fMRI signal may also reflect changes in neuronal synchrony without a concomitant rise in mean firing rate (Fries et al., 2001). These confound the measurement of the fMRI signal. Without a measure of the neuronal electrical activity, it is difficult to resolve this issue and say whether fMRI signal changes occur due to the neuronal firing, vascular response or both. Logothetis et al. (2001) simultaneously measured neuronal activity and the hemodynamic response to study how these factors are related. It was found that the BOLD response in primates directly reflects an increase in neural activity, correlating particularly with local field potentials (LFP - represent synchronized synaptic inputs of a given neuronal population). The Logothetis study (2001) examined how well fMRI measurements could be predicted from LFP and multi unit activity (MUA – reflects spiking activity of neurons near the electrode tip) and found that on average, LFP was better than MUA in predicting fMRI responses. Interestingly, they found that the fMRI responses increased much more rapidly than neuronal responses at low stimulus contrasts, but less rapidly at higher contrasts. In other words, they observed a non-linear relationship between LFP and the BOLD signal. Other studies have compared human fMRI and monkey single-unit data to infer that fMRI signals are directly proportional to average neuronal firing rates (Rees et al., 2000; Heeger et al., 2000). Rees et al. (2000) found that the average neuronal firing rates (calculated from single-unit data in macaque MT) and fMRI measurements from human MT complex (V5) increased approximately linearly with motion coherence of visual stimuli. Heeger et al. (2000) also did similar comparisons between fMRI measurements from human primary visual cortex (V1) and single unit data from monkey V1 using stimulus contrast as the independent variable and

reported a proportional relationship between average neuronal firing rate and the fMRI signal. The above studies thus found that in two different cortical areas (V1 and MT), fMRI responses are proportional to average firing rates, although with different proportionality constants. A 1% change in fMRI signal corresponded to an average firing rate of 9 spikes/sec in monkey MT while in human V1 it was 0.4 spikes/sec (for an explanation of this difference in humans and monkeys see Heeger et al., 2000). The important result of these studies is that the hemodynamic response shows a roughly linear relation to the underlying neuronal activity (see also Boynton et al., 1996; Buckner, 2003). However, this relation does not hold true always, especially in higher order visual areas in cats. Harel et al. (2002), found that spike activity in the visual areas increased in response to moving gratings, but cerebral blood flow (CBF) did not increase and sometimes even decreased. Hence it is possible that other factors such as local distribution of blood flow within the vascular network may regulate the BOLD signal (Harrison et al., 2002). In addition, it should also be borne in mind that the fMRI signal as measured, is presumably proportional only to the local firing rate averaged over a small region of cortex and a short period of time. This raises two issues of the fMRI signal, namely the spatial and temporal resolution.

1.3.4. Spatial resolution

Typical in-plane spatial resolution in human fMRI studies is 3-5 mm, which is better than PET and single photon emission computerized tomography (SPECT) (Kim et al., 2000b). However, the localization of the BOLD signal depends on the spatial relation of voxels in the region of interest to adjacent vessels. We know that the BOLD effect

is manifested in the capillary beds, venules and draining veins, which are only 60-70% saturated with oxygen at rest, and hence have the capacity to become more oxygenated. The size of the vessels giving rise to the fMRI signal thus varies from the capillary bed ($<10\text{ }\mu\text{m}$) to draining veins (a few mm) (Menon, 1993; Lai S et al., 1993, Lee et al., 1995) and the signal from the latter can be displaced by several millimeters from the site of neuronal firing (Kim et al., 1994; Frahm et al., 1994; Kim et al., 1994). Given the complex nature of the BOLD signal and the influence of large draining veins on the location of the observed signal, it is desirable to obtain higher spatial resolution for the signal. Improving spatial resolution of the fMRI signal means localizing neuronal activity more precisely. Malonek & Grinvald (1996) using optical imaging techniques, exploited the initial dip to achieve high spatial resolution and delineate even the columnar structure of the cat visual cortex. The initial dip, as mentioned above, occurs due to immediate oxygen utilization after neural activity, and hence is quite localized compared to the ensuing blood flow, which occurs at a much coarser spatial scale. Malonek & Grinvald (1996) referred to this delayed increase in cerebral blood flow as “watering the garden for the sake of one thirsty flower”. Evidence that tissue oxygen utilization also followed this pattern came from Thompson et al. (2003). They found that an initial dip occurred only in cortical columns, which responded maximally to the stimulus while the neighboring columns exhibited a robust positive peak in oxygen response without an initial dip. Hence the initial dip not only provides evidence for uncoupling between neural activity and blood flow, but also offers a temporal window for mapping signals at higher spatial resolution. This potential of the initial dip for mapping columnar structure was

exploited by many fMRI studies. It is not surprising that most of these fMRI studies used high field strength magnets in the order of 4.7T (Menon et al., 1997; Menon & Goodyear, 1999; Duong et al., 2001, Kim & Duong, 2002; Kim et al., 2000a), as higher spatial resolution appears to derive from higher intrinsic signal, which is obtained by using high field magnets.

Factors other than physiological, contribute to improved spatial resolution of the fMRI signal (for a detailed discussion, please see Kim et al., 2000b). Issues to be considered include task-induced signal change to signal fluctuation ratio and minimization of large vascular contributions using different imaging parameters. In addition to technical limitations that restrict spatial resolution, biological variables may play a role. For instance, vascular supply is not regulated on the scale of individual neurons and the neural-hemodynamic coupling varies between species, people and even between different areas of the brain (Menon & Kim, 1999). A combination of these factors may prescribe the limits to which this technology can be pushed to achieve better spatial resolution.

1.3.5. Temporal resolution

Temporal resolution has been defined in several ways in the literature which includes the image acquisition rate, the time it takes for activation-induced response to rise or fall a given amount, the maximum rate at which activation can be turned on and off and the smallest detectable activation duration (for details of these definitions, refer Bandettini, 2000). Early fMRI studies used the block design and collected minute long epochs of averaged brain activity. The next chapter in this dissertation describes

an fMRI study on motor coordination, in which we collected six minute long epochs comprised of 30 sec blocks of activity and rest (Nair et al., 2003). One of the notable advances in improving the temporal resolution of the fMRI signal was event-related fMRI (Buckner et al., 1996; McCarthy et al., 1997; Friston et al., 1998), which allowed identification of brain signals induced by individual cognitive events - for instance to distinguish brain activation during go and no-go trials of a go/no-go paradigm. Analysis techniques such as selective averaging (Dale & Buckner, 1997) and multiple regression (Clarke et al., 1998), offered the possibility of separating brain responses by using rapidly presented, mixed trials. In chapters 4 and 5 of this dissertation, we describe experiments in which we presented subjects with two alternate stimuli or tasks in a single scanning epoch. Multiple regression was used to study the relative contribution of these stimuli/tasks to the overall pattern of neural activation. Boynton et al. (1996) used manipulations of contrast and timing of visual stimuli to show that the duration and amplitude of the hemodynamic response were respectively proportional to changes in duration and amplitude of neural activity. This had important implications in finding solutions to the hemodynamic inverse problem (Buckner, 2003), in that temporally shifted hemodynamic responses could represent delays in underlying neuronal activity, especially given the linear relation between the two (Boynton et al., 1996; Heeger & Ress, 2002). Bellgowan et al. (2003) tested this idea in a 3T fMRI study using a lexical decision task, and found that the hemodynamic timing estimates of certain brain regions correlated with timing delays induced by the cognitive demands of the task. For instance, prefrontal cortex showed an onset delay proportionate to the rotation of letter strings and also during

comparison of non-words with words. Kim and colleagues (Richter et al. 1997a,b) introduced what they call “time-resolved fMRI” to identify the temporal sequence of neuronal activation when subjects performed certain tasks. The essential idea behind this was that, a variable behavioral parameter (such as reaction time) could be correlated with a measure of the time series (onset time or width of the response), to give more information on the time at which a particular brain area was involved in a task. It must be noted here that these studies recorded single trial data at 4T, because at high magnetic fields it is possible to monitor fMRI signal evolution in a single execution of a task without averaging over many trials. If averaging becomes necessary, it is usually done by aligning the responses with respect to a behavioral correlate, such as the reaction time. This method of improving the temporal resolution of the fMRI signal is based on the tenet that brain areas activate in a temporal order. Evidently, this applies only to hierarchical networks that use a sequential mode of information processing (as may be the case of simple tasks, without involving higher order semantic processing) and may not be applicable for many other neural networks, where information processing occurs in parallel. In addition to manipulations of imaging parameters, use of fMRI with other imaging modalities such as MEG and EEG will improve our understanding of the temporal nature of activation and hence aid in identification of neural loops involved in the task.

1.3.6. Negative BOLD

Considering the sequence of events that follow neural excitation, one of the following possibly contribute to a negative BOLD signal – a) larger fractional increase in

cerebral metabolic rate of O₂ compared to cerebral blood flow; b) a larger fractional decrease in blood flow compared to cerebral metabolic rate of O₂; c) a delay in blood flow to the region causing the initial dip to be prolonged. As we have seen earlier, the first possibility, which is a larger fractional increase in cerebral metabolic rate of O₂ compared to cerebral blood flow, does not occur in the brain with neural activity. Harel et al. (2002) examined the second possibility of a larger fractional decrease in blood flow, by studying blood volume changes using injections of monocrystalline iron oxide nanoparticle (MION) as a contrast agent. They suggested a vascular “steal” effect in which blood is diverted or allocated to the most active areas while adjacent areas exhibit a decrease in blood flow. However, a few observations fail to give ample support for this steal phenomenon. First, the cerebral vascular reserve is so large compared to changes in blood flow associated with the task, that there is little reason to “steal” from other adjacent areas. Second, the decreases can occur remote from the site of increases (Shulman et al., 1997) making a local vascular steal almost impossible. Röther et al. (2002) examined the third possibility, which is a delay in blood flow to active neural regions. They studied a patient with impaired cerebrovascular reserve capacity due to transient ischemic attack and observed a prolonged negative response prior to the positive response. They argued that this prolonged negative response was due to persistent deoxyhemoglobin arising out of the absence of an immediate hemodynamic response. Hence in conditions of impaired cerebral blood flow or impaired autoregulation, cerebral blood flow and metabolism may be uncoupled not only for a few seconds, but for longer periods of time, till the hemodynamic coupling has taken place.

Previous studies have also suggested that the negative signal change is due to inhibition or suppression of neuronal firing (Raichle, 1998). Such task-induced deactivation has been observed in many neuroimaging studies (Shulman et al., 1997; Binder et al., 1999) and implies that there is more blood flow during “rest” than during the task. The crucial idea here is that “rest” does not necessarily mean a period of inactivity, but a cognitively rich state characterized by a variety of possible attention-dependent processes. These attention demanding processes include verbal and visual imagery, planning and problem solving, monitoring the external environment, monitoring the internal sensory state and body image, monitoring emotional state, encoding and retrieval of episodic memory and working memory (see Gusnard & Raichle 2001 for a review; McKiernan et al., 2003). The evolutionary implications and the need for such processes in the resting state are quite evident. Areas that deactivate during a task do so because other actively involved areas (specific to the task) require attentional input to stay active. Thus when attentional resources are relocated from areas, which are active during rest, they become deactivated. McKiernan et al. (2003) tested this hypothesis by parametrically manipulating task difficulty and found that task difficulty indeed determined the extent of resources to be allocated and hence, the amount of deactivation seen.

1.3.7. fMRI and the study of clinical disorders

Over the last couple of years, fMRI has been increasingly used to study neurological and psychiatric diseases, pre-operative evaluation of patients with intractable epilepsy

(to determine the lateralization of language and memory) and localizing the epileptic focus (Hammeke, 2000). Being non-invasive and free of radiation hazards, fMRI is ideal for studies on the clinical population. Monitoring brain function over time using the same task, allows one to examine different patterns of neural activity that emerges as the connectivity between areas changes with recovery of function. This throws more light on the compensatory mechanisms that happen in the brain in order to improve function in these functionally compromised states. Results from our study on a stroke patient (chapter 3) provide evidence for the cooperative action of several cortical regions within and even across hemispheres, to help recover from the neurological insult. In chapter five, we discuss the neural mechanisms of motor coordination and timing in Parkinson's disease patients and age-matched control subjects. The results not only highlight the importance of such studies in understanding compensatory mechanisms in the brain including changes in functional connectivity, but also help us formulate new methods of treatment for these patients.

Chapter 2

Cortical and cerebellar activity during imagined and executed unimanual and bimanual action sequences

2.1. Introduction

A majority of studies aimed at understanding the neural correlates of goal-directed action, has focused on the activation of individual brain areas, such as the sensorimotor cortex, the Supplementary Motor Area (SMA) or the cerebellum. In this study, using fMRI of the entire brain, we aim to furnish a more complete view of brain activation during finger-sequencing tasks. We compare brain activation during overt and imagined movements, both unimanual (left and right hand separately) and bimanual (both hands sequencing together).

A complex movement task such as sequential finger movement involves many processes, including movement planning, selection, prediction and execution, whereas imagery of the same task requires the same set of processes, except the last. Due to this inherent difference in the nature of the two tasks, one should expect differences in brain activation. The question of whether motor execution and imagery share common neural resources has been addressed by many studies in the recent past. Significant increases in fMRI signal intensity were observed in the pre-central (Primary motor cortex, M1) and the post-central gyri (primary somatosensory cortex, S1), during both motor performance and imagery of a finger-to-thumb opposition task (Porro et al., 1996). The same task induced activation in contralateral M1, S1 and pre-

motor cortices during actual execution but only in M1 and premotor cortex during mental simulation in another study (Roth et al., 1996). When subjects were asked to make fists and then imagine doing the same, increased fMRI signal intensity was observed in M1, premotor cortex and the SMA during both execution and imagery tasks, with S1 showing significantly less activation during imagery (Luft et al., 1998). Cerebral blood flow measured using PET was observed to increase in medial and lateral premotor areas as well as cingulate motor area (CMA) during both execution and imagery of joystick movements (Stephan et al., 1995). The latter study also reported additional activation in primary sensorimotor cortex and rostral superior parietal lobe during task execution (Stephan et al., 1995). Compared to actual motor performance, imagery appears to produce significantly lower fMRI signal changes in the cerebellum (Luft et al., 1998; Lotze et al., 1999). Although these studies used different tasks - making fists (Lotze et al., 1999) and finger to thumb opposition (Luft et al., 1998), both reported differential activation of the cerebellum during execution and imagery: strong activation of the anterior cerebellum was observed during execution while imagery resulted in posterior lobe activation. Movement execution thus seems to engage a large network of brain areas including the M1, S1, premotor areas (SMA, CMA), superior parietal lobule and the cerebellum. Imagery of the same movements seems to engage almost all these areas, although the intensity of activation appears to drop off in S1 and cerebellum.

Unimanual and bimanual tasks employ overlapping as well as different neural resources (Jäncke et al., 1998). In right-handed individuals, the right sensorimotor

cortex was found to be more active than the left in unimanual finger sequencing tasks, whereas the left showed more activation than the right sensorimotor cortex during bimanual tasks (Jäncke et al., 1998). For both unimanual and bimanual tasks, the area and intensity of brain activation appear to increase with task complexity, force and rate of movement (Jäncke et al., 1998; Jäncke et al., 1999; Rao et al., 1993; Rao et al., 1996; Schubert et al., 1998; Shibasaki et al., 1993; Toyokura et al., 1999; Wexler et al., 1997). SMA, pre-SMA and CMA have been implicated in the control of complex finger movements (Dassonville et al., 1998; Deiber et al., 1999; Jäncke et al., 2000; Kim et al., 1993; Shibasaki et al., 1996). Comparing repetitive tapping of the index finger with sequential movement of fingers, Wexler et al. (1997), found that the parietal lobe, especially the superior parietal area, was selectively activated in the more complex finger-sequencing task. In self-paced finger movements, however, cortical structures around the intra-parietal sulcus were activated (Schubert et al., 1998). The intra-parietal sulcus is also active when finger movements are coordinated with reference to a specific spatial reference (Binkofski et al., 1999; Jäncke et al., 2001). It appears that the parietal cortex is involved in a wide variety of tasks, especially those in which subjects need to access spatial information and spatial memory. Since unimanual and bimanual tasks basically differ in the involvement of one versus two hemispheres, studies have focused on the laterality of brain activation during such tasks. In right-handed individuals, significant ipsilateral (left) motor cortex (M1) activation is observed during movement with the non-preferred (left) hand (Kim et al., 1993; Singh et al., 1998). Such ipsilateral activation for movement of the non-dominant hand has been attributed to task complexity (Rao et al., 1993).

Similarly, some studies have reported bilateral cerebellar activation when right-handed subjects moved used their non-dominant left hand (Ellerman et al., 1994; Jäncke et al., 1999). These findings suggest that when subjects perform tasks with their non-dominant hand, an additional neural loop consisting of motor areas of both the hemispheres is involved, that facilitates coordination of motor behavior.

In the present study, we aim to identify the brain areas involved in both overt finger sequencing and imagery alone conditions. Following Jäncke et al. (1998) we studied differences in brain activation between unimanual and bimanual finger movements. Here, however, instead of using a simple finger-sequencing (2345) task, a different movement sequence was prescribed for each task (left, right and bimanual conditions) in order to minimize or at least balance effects due to learning, and to control for task difficulty across exemplars of the task. By imaging the entire brain during these tasks, our main goals were twofold: First, to understand how cortical and cerebellar areas are differentially engaged during the course of motor performance and imagery. In particular, we expected on the basis of older (Kelso & Stelmach, 1976) and more recent models of motor control (Wolpert & Ghahramani, 2000) which posit extensive internal feedback and feedforward cerebro-cerebellar loops, that cerebellar involvement will be greater during active, planned than imagined movement sequences. This is because of the putative role of the cerebellum in correcting errors in motor commands prior to their effects at the periphery. Our second goal was to clarify the role of parietal and other cortical areas in movements such as complex bimanual action sequences, which incorporate spatial information and spatial

memory. In particular, evidence from patients with parietal lesions suggests frank motor imagery deficits (Jeannerod & Decety 1995; Crammond, 1997). On this basis, we might expect greater parietal involvement as the task becomes more difficult to imagine, such as when the non-preferred hand is used or when both hands are sequencing together.

2. 2 Materials and Methods

2.2.1 Subjects

In this study 8 healthy right-handed volunteers participated, 3 males and 5 females, aged 25-40 years. Informed consent was obtained from all subjects. Handedness was determined by simple inquiry, consisting of a few questions from the Edinburgh Handedness Inventory. All subjects were neurologically intact. No one reported any psychiatric or cardiovascular illness and none was on medication.

2.2.2. Task

The experiment consisted of three conditions, two unimanual and one bimanual. During the unimanual condition, subjects performed movements with the right or left hand alone, whereas the bimanual task was carried out using both hands simultaneously. During the experiment, the hands were kept in a semi-prone position, by the subject's side, so that the experimenters were able to see the subject's finger movements at all times (and lack of such during imagery conditions). The fingers were labeled 1 to 5 from the thumb to the little finger (anatomical convention) and the

sequences were 5342, 2435 and 4253 for left, right and bimanual conditions respectively. Task instructions were given to subjects just before the beginning of each experimental condition. Subjects were asked to keep their eyes closed during the entire experiment and to concentrate on the task, opposing thumb to fingers as fast, firmly and accurately as possible. Subjects were monitored throughout the experiment for movement speed and precision. Each experimental condition consisted of overt movement of the fingers in a prescribed sequence and imagery of the same task. For the latter, subjects were instructed to imagine making the requested finger sequences as quickly and as accurately as possible, and to remain relaxed without moving their fingers. The order of conditions was randomized across subjects.

2.2.3. Image acquisition protocol

Whole brain fMRI data acquisition was carried out using a 1.5 Tesla Signa scanner (General Electric Medical Systems, Milwaukee, WI), equipped with echo planar imaging (EPI) capabilities. Images were acquired with the participants lying supine inside the scanner. Before entering the scanner, subjects were briefed about the tasks to be performed. The sequence of finger movements was explained to them when they were inside the scanner. Each condition (unimanual and bimanual) lasted for 4 minutes, and was comprised of 4 periods of activation (ON, task) during which subjects performed the task and four baseline (OFF, rest) periods in which subjects heard only the ambient machine noise. Alternating periods of task and rest were cued to the subject through instructions to “move” and “rest” respectively, delivered through a microphone. The two phases of each condition: overt movement (right, left

and bimanual) and imagery (right, left and bimanual) lasted 12 minutes each. Throughout the experiment, the subject's head was supported by a comfortable foam mold. Head movement was further minimized using foam padding and forehead restraining straps.

Scanning started with the acquisition of full head, 3D SPGR (spoiled gradient) anatomical images, with the following imaging parameters: Field of view (FOV) = 26cm, frequency-phase matrix = 256 x 256, repetition time (TR) = 34ms, echo time (TE) = 5 ms, flip angle (FA) = 45°, slice thickness 2mm, and one excitation per phase encoding step. For each subject, T2*-weighted gradient echo, echo planar multi-slice datasets were acquired during performance of the finger sequencing tasks. (TR = 3000ms; TE = 60 ms; FA = 90 degrees; 20 axial slices, frequency-phase matrix = 64 x 64; FOV = 24 cm; slice thickness = 5 mm and inter-slice gap = 2.5 mm). Thus the voxel size was 3.75 x 3.75 x 7.5 mm. High-resolution background images (same 20 slices, frequency-phase matrix size = 512 x 512) were also acquired for overlaying the functional data.

2.2.4. Data analysis

The software packages used for data analysis were AFNI (Analysis of Functional NeuroImages, Medical College of Wisconsin (Cox, 1996)) for display and analysis, and SPM (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, London) for coregistration. For each subject the following steps of analysis were performed:

1. Movement correction of the functional datasets using the Fourier method in AFNI (Cox & Jesmanowicz, 1999).
2. Cross-correlation with a boxcar reference function (30 sec on, 30 sec off) which was shifted by 6 sec to account for the delay of the hemodynamic response. This shift was determined by examining the raw time series data. AFNI creates a dataset, which contains two numbers per voxel representing the cross-correlation value (a number between -1 and 1) and the intensity.
3. Masking out all voxels with a cross-correlation (with zero-time lag) of smaller than 0.5 leads to datasets of intensities for active voxels only;
4. Coregistration and reslicing of the high-resolution background images and the intensity dataset with a full-head T1-weighted scan with cubic voxels of 2 mm (done in SPM);
5. Transformation into Talairach stereotaxic space (Talairach & Tournoux, 1988);
6. Identification of clusters of active voxels using cluster size thresholding. The minimum volume for a cluster was determined using the AlphaSim module in AFNI. This procedure uses Monte Carlo simulations to create random datasets in order to determine the probability of finding activations due to chance. With the underlying assumption that such activity is more likely in single voxels than clusters of voxels, probability values are calculated for clusters with different volumes and active voxels within a certain distance (Xiong et al., 1995). In our case, these values turned out to be 4mm for the distance

between active voxels and a volume of 40 μ l in order to achieve an overall significance of $p < 0.01$.

In individual subjects, brain areas with active clusters were identified by their coordinates in Talairach stereotaxic space using the “Talairach daemon”, a web based interactive program that reads out the brain area when the coordinates of a voxel are given (Lancaster et al., 1997). Once clusters were identified in the individual data (for every condition and every subject) these data were subjected to a two-way analysis of variance (ANOVA) using ‘hand’ (three levels – left, right, bimanual) and ‘state’ (two levels – movement and imagery) as the two crossed factors. Significant voxels were overlaid in color over the anatomy with positive activations, i.e. higher MR signal amplitude during task compared to rest, ranging from red (minimum) to yellow (maximum) and negative activations ranging from blue to cyan.

2.3. Results

All subjects performed the task sequences correctly at movement rates that were quite similar across subjects. No overt movement was observed during the imagery tasks. During post-experiment interviews in which subjects were asked to evaluate their performance, some subjects reported that imagining bimanual sequences was the most difficult task.

2.3.1. Group Analysis

ANOVA revealed a main 'hand' effect ($F(2, 42) = 5.14$; at $p < 0.01$) in bilateral pre- and post-central gyri. Similarly, a main effect of 'state' ($F(1, 42) = 7.28$; $p < 0.01$) was also found in bilateral pre- and post-central gyri, SMA, bilateral parietal lobe, bilateral precuneus and bilateral cerebellum. The interaction ($F(2, 42)$) between hand and state was also significant ($p < 0.01$). In the following, we unpack this interaction using conservative ($p < 0.01$) post-hoc t-tests.

2.3.1.1. Execution - Bimanual versus unimanual

Post-hoc analysis revealed greater activity for bimanual than left-handed movements in the left sensorimotor cortex, bilateral superior parietal lobules, supplementary motor area (SMA) and bilateral cerebellum. Fig 2.1a shows enhanced activity in the right precuneus and the right precentral gyrus, fig 2.1b shows increased activity in the left sensorimotor area, SMA and the left precuneus, and figs 2.1c and 2.1d depict greater activity in bilateral cerebellum during bimanual action sequences. Significant differences ($p < 0.01$) were also found between bimanual and right-handed finger movements in the right sensorimotor cortex, SMA, left precuneus, and bilateral cerebellum. Fig 2.2a shows enhanced activity in the right sensorimotor cortex, SMA and left precuneus. Figs 2.2b and 2.2c show higher intensity activation in bilateral cerebellum during bimanual action sequences.

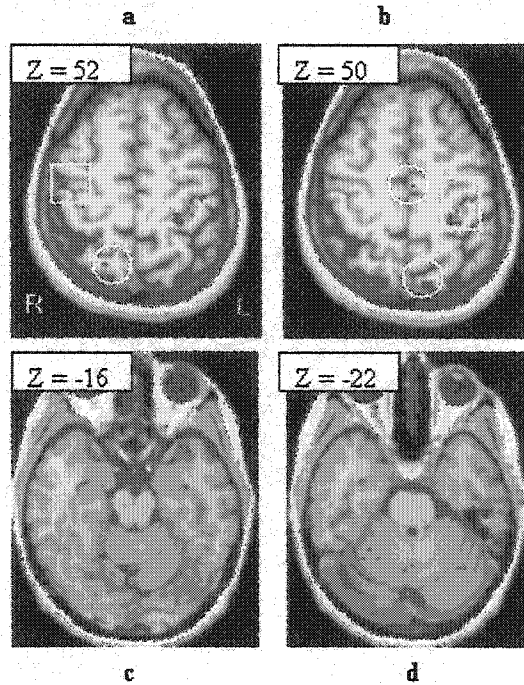


Fig 2.1. Comparison of bimanual versus left-handed execution of finger sequences yielded significantly greater activity ($p < 0.01$) in the right pre-central gyrus (square, fig a), right precuneus (oval, fig a), left sensorimotor cortex (square, fig b), left precuneus (yellow oval, fig b), SMA (white oval, fig b), and bilateral cerebellum (colored voxels, fig c and d). Activity is overlaid on a representative individual brain. The Z values show the slice position along the vertical axis in the Talairach coordinate system. R and L indicate the right and the left side respectively.

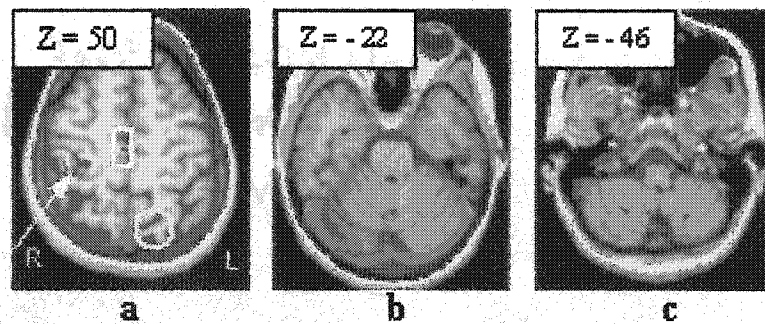


Fig 2.2. Comparison of bimanual versus right-handed execution of finger sequences yielded significant voxels ($p < 0.01$) in the left precuneus (yellow ellipse, fig a), right sensorimotor cortex (arrow, fig a), SMA (rectangle, fig a) and bilateral cerebellum (colored voxels in figs c & d). Greater activity (voxels in red) is observed during bimanual than right-handed action sequences.

2.3.1.2. Execution - Unimanual differences: left versus right

A comparison of left and right-handed movement sequences revealed significant ($p < 0.01$) voxels in right sensorimotor cortex, SMA and left cerebellum (and corresponding negative differences in the left sensorimotor cortex and right cerebellum). The red and yellow voxels in fig 2.3a show enhanced activity in the right sensorimotor cortex and SMA during left-handed action sequences, while the blue voxels depict enhanced activity in the left sensorimotor cortex during right-handed action sequences. Fig 2.3b shows enhanced activity in the left, ipsilateral cerebellum (red voxels) during the left-handed sequencing task and also in the right cerebellum during the right-handed task (blue voxels).

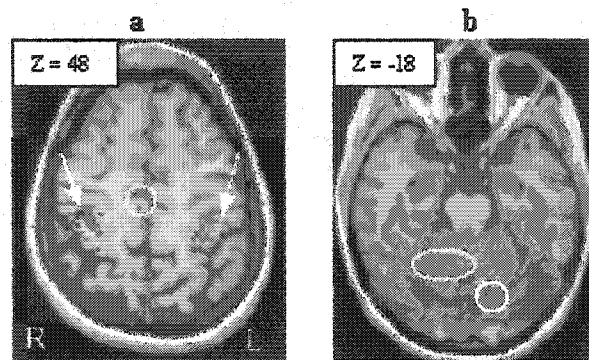


Fig 2.3. Comparison of left versus right-handed execution tasks. The right sensorimotor cortex (white arrow, fig a), SMA (yellow oval, fig a) and the left cerebellum (white oval, fig b) have more activation during left-handed than right-handed execution and the left sensorimotor cortex (yellow arrow, fig a) and right cerebellum (yellow oval, fig b) show more activity during right hand execution.

2.3.1.3. Imagery versus Execution

Comparison of left-handed execution and imagery tasks revealed significantly active voxels ($p < 0.01$) in the right sensorimotor cortex, SMA, and the left cerebellum (fig

2.4). The colored voxels in figure 2.4 depict enhanced activity in SMA, right sensorimotor cortex (fig 2.4a) and left cerebellum (fig 2.4b) during left-handed execution. A similar comparison between executed and imagined right-handed sequences revealed significantly active voxels in the left sensorimotor cortex, left superior parietal lobule (fig 2.5a) and the right cerebellum (fig 2.5b). Significant differences between bimanual execution and bimanual imagination tasks were observed in bilateral sensorimotor cortices, bilateral precuneus, SMA, bilateral inferior parietal lobules, and bilateral cerebellum (fig 2.6). Enhanced activity in bilateral sensorimotor cortices and SMA can be seen in fig 2.6a and 2.6b, right precuneus in fig 2.6a, left precuneus activity in fig 2.6b, bilateral inferior parietal lobules in fig 2.6c, and bilateral cerebellum in fig 2.6d.

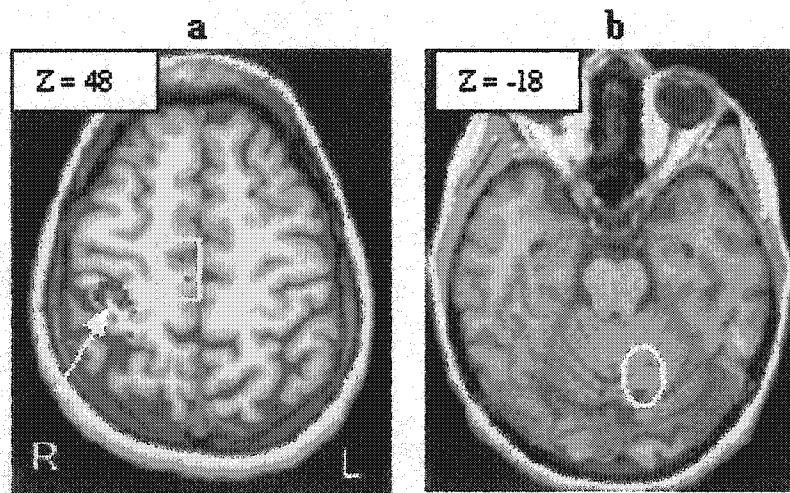


Fig 2.4. Comparison of left-handed execution versus left-handed imagined tasks. Significantly greater activation ($p < 0.01$) was observed in the right sensorimotor cortex (arrow, fig a), SMA (rectangle, fig a), and the left cerebellum (white oval, fig b) during execution.

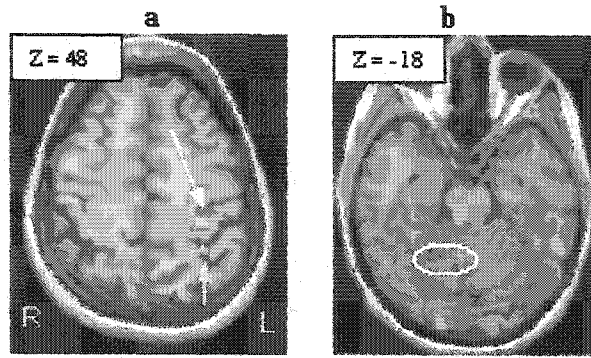


Fig. 2.5. Comparison of right-handed execution versus right-handed imagery shows significant differences ($p < 0.01$) in the left sensorimotor cortex (white arrow, fig a), left superior parietal lobe (yellow arrow, fig a) and the right cerebellum (oval, fig b) indicating greater activation during execution.

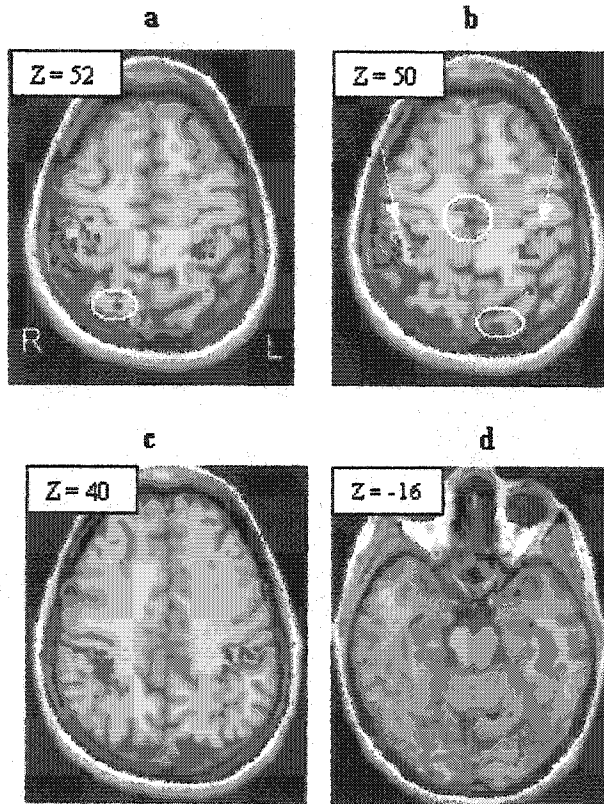


Fig. 2.6. Comparison of bimanually executed and imagined action sequences resulted in greater activation in right precuneus (yellow oval, fig a) bilateral sensorimotor cortices (yellow arrows, fig b), SMA (white oval, fig b), left precuneus (yellow oval, fig b), bilateral parietal lobes (fig c), and bilateral cerebellum (fig d) during the bimanual execution task.

2.3.2. Individual Analysis

Variability in brain activation is to be expected among subjects. Fig 2.7 provides an “activation grid” which depicts brain activation (hatched regions) in our subjects during the six tasks. The top row of the figure shows activity during the three execution tasks (left, right and bimanual) and the bottom, activation during imagery tasks. The numbers on the Y-axis represent individual subjects 1-8; RM and LM – Right and Left Primary motor area; RS and LS – Right and Left Primary somatosensory area; SM – Supplementary Motor Area; RP and LP – Right and Left Superior Parietal lobule; RC and LC– Right and Left Cerebellum. It can be seen that cerebellar activity (last two columns) in most of the subjects drops off during the imagery tasks. Subjects show maximum activation during the bimanual execution task (top right).

Clusters of brain areas active for all subjects during execution and imagery conditions were tabulated to examine similarities in patterns of neural activation. Table 2.1 gives the number of subjects with activation in different brain areas during all six tasks. The rows depict individual brain areas and the six columns represent the six tasks. Two asterisks indicate seven or more subjects, a single asterisk indicates 4-6 subjects and a blank cell indicates that only three or fewer subjects showed activation in that particular brain area. Maximum activation was seen in all areas during the bimanual execution task (5th column). There is more ipsilateral activation in the sensorimotor cortex during the left (non-preferred hand) movement task than the right-handed (preferred hand) movement task (compare columns 1 and 3). A general reduction in

activity was observed during the imagery tasks, especially in the somatosensory cortex and the cerebellum (columns 2, 4 and 6). SMA was consistently active during both movement and imagery tasks (row 3), whereas activity in the cerebellum dropped off markedly during the imagery tasks (compare data in columns 1 and 2, columns 3 and 4, columns 5 and 6).

Brain area	Lt_move	Lt_image	Rt_move	Rt_image	Bi_move	Bi_image
R. M1	**	*	*		**	*
L. M1	**	*	**	*	**	*
SMA	**	**	**	**	**	*
R. S1	**		*		**	
L. S1	*		*		**	
R. SPL	*	*	*		**	*
L. SPL	**	*	*	*	**	*
R. CII	**		**		**	*
L. CII	**	*	**		**	*

Table.2.1 shows the number of subjects with activation in different brain areas during the six tasks. The letters L and R indicate left and right hemisphere respectively. M1 – Primary motor area, SMA – Supplementary Motor Area, S1 – Primary Somatosensory area, SPL – Superior Parietal Lobule, CII – Cerebellum. The following schematic representation is used to denote the number of subjects showing activation in a brain area: 3 or less by blank; 4-6 by an asterisk (*); and 7 or more by two asterisks (**).

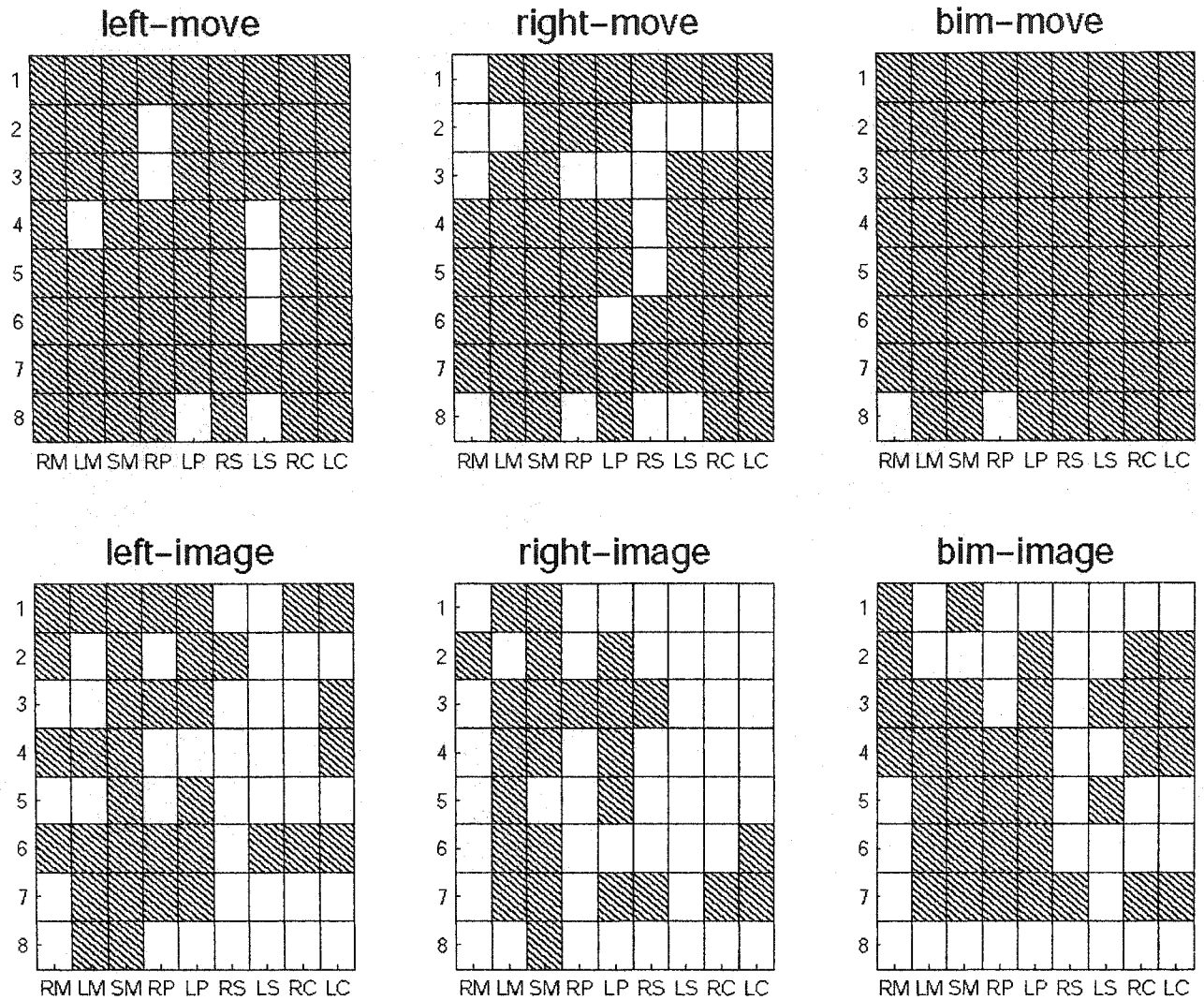


Fig.2.7. Shows an "activation grid" which depicts brain activation (hatched regions) of all subjects during the six tasks. The top row shows activity during the three execution tasks - left, right and bimanual (indicated by left-move, right-move and bim-move respectively). The bottom row shows activity during imagery tasks (indicated by left-image, right-image and bim-image). The numbers on the Y- axis represent individual subjects 1-8. R and L in the X- axis denote the right and left hemispheres; M1 - Primary motor area; S1 - Primary somatosensory area; SMA - Supplementary Motor Area; P - Superior Parietal lobule; C1 - Cerebellum.

2.4. Discussion

Given the complexity of voluntary movement, both in terms of the selective engagement of neuroanatomical structures in time and the vast repertoire of behaviors possible, it is reasonable to assume that an intricate network of cortical and sub cortical structures is involved, especially in fine movements such as finger sequencing. Definitive answers are clouded, however, by the wide variety of tasks employed and because the same set of task components is seldom studied in the same subjects. Two important points may be gleaned from the diverse activations observed in different studies: (i) the brain activation observed depends largely on the nature of the task; and (ii) seemingly complex tasks require the recruitment of a larger and more intricately connected network of brain areas.

A key feature of the present experimental design was that the same subjects were examined in a spatiotemporal sequencing task that isolated the dimensions of handedness (left and right), manual engagement (unimanual and bimanual) and cognitive influences (imagined and executed) on action. Overall effects of these manipulations are present in the brain, as well as interesting differences among individuals in the way neural areas are engaged and disengaged in sequential tasks.

As expected, activation in cortical and cerebellar regions of the brain is associated with the planning and execution of spatiotemporal actions. Pre- and post-central gyri, SMA, parietal cortex and cerebellum are all recruited to differing degrees in active, self-generated action sequences. These regions are certainly necessary, if not sufficient, for this kind of task. Examination of individual data revealed that bilateral primary motor cortex was activated more prominently when the task was performed

with the non-preferred left hand (fig. 2.7 and Table 2.1). This, along with the fact that ipsilateral motor cortical activation was greater in the left hand, suggests that subjects' reported difficulty in performing action sequences lies at the executional level. Notably, SMA is similarly engaged in all movement conditions, in all subjects. An interesting finding was that the superior parietal lobules are involved especially, though not uniquely, in coordinating bimanual sequences. It is reasonable to assume, in accordance with our subjects' verbal reports, that bimanual sequential actions place greater demands on attention and memory, as well as execution. A considerable amount of evidence implicates parietal cortex in the execution of hand movements (Crammond, 1997). Relatedly, our results showing that parietal cortex is significantly more active in bimanual and left-handed execution relative to imagery conditions, suggest a connection between parietal cortex and task difficulty (Wexler et al., 1997). In both execution and imagery tasks, subjects had their eyes closed and hence had to rely on knowledge of the spatial dimensions of the task along with the sensory feedback that they experienced during movement. Accessing this memorized spatial information may result in the precuneus activation observed in our subjects during execution and imagery.

Imagining and performing coordinated movements engage SMA and Superior parietal cortex to varying degrees. Only in actually performed action sequences are pre-central, post-central and cerebellar cortices active. These results taken in tandem suggest that both unimanual and bimanual actions involve a distributed network that, at the very least, engages all these areas. The actual time-dependence of this process cannot be assessed using fMRI alone. However, in conjunction with multi-channel

MEG and EEG recordings, deeper insights into the spatiotemporal dynamics of the human brain may well emerge (Jirsa et al., 2001). In light of previous evidence it seems likely that SMA is involved in the planning and preparation of action sequences whether real or imagined. Parietal cortex (especially the Superior Parietal Lobule, Brodmann's area 7, the precuneus) is engaged most especially for bimanual action sequences that rely on remembering and executing the correct ordering of task components along with processing the sensory consequences of action.

A key result is that sensorimotor cortical and cerebellar areas appear to be functionally decoupled from the task network when people imagine but do not actually execute sequential actions. The suppression of activity in these areas and their corresponding activation during normal movement suggests the involvement of a cerebro-cerebellar internal feedback loop. From clinical studies, the latter has long been implicated in the initiation and control of voluntary movement. The crucial idea is that feedback is generated internally ("corollary discharge") not only from peripheral receptors as a consequence of muscular contraction (Ghez, 1991; Kelso & Stelmach, 1976). Long ago, Oscarsson (1965) identified a functional role for interneuronal pools that carry specific information from descending motor paths. His work on the functional organization of spino- and cuneocerebellar tracts promoted the hypothesis that the anterior lobe of the cerebellum is important for correcting "errors" in motor activity elicited from the cerebral cortex. The cerebellum was seen as receiving information about command signals from the motor cortex, the effects these signals evoke on lower motor areas that are also influenced by peripheral afferents,

and the evolution of action as conveyed by extero- and proprioception. Massive interconnectivity between cerebral cortex and cerebellum led Ito (1970) to propose that cerebellum monitors cortical output and feeds back corrective information well before cortical output gives rise to activity in motor neurons. Resulting sensory information may then act to stabilize movement via afferent feedback connections to the post-central cortex (Kelso et al., 2001). Such notions figure prominently in modern computational models of motor control, which posit a role for “internal modeling”, as a way to circumvent peripheral delays once movements are highly practiced (receptors as a consequence of muscular contraction (Ghez, 1991; Kelso & Stelmach, 1976; Wolpert & Ghahramani, 2000). Our data suggest rather strongly that only intended and realized action sequences engage this hypothesized cortico-cerebellar loop. Sans actual movement there is little or no observed cerebellar activity, whether in control signals from motor cortex or as a result of information processing in post central receiving areas.

It is clear from the present work that the brain engages multiple cortical and cerebellar structures to varying degrees for planned sequential action. More and more evidence points to the brain as a highly interconnected, spatiotemporal dynamical system that uses distributed representational schemes (Edelman & Tononi, 2000; Friston, 2000; Haken, 1996; Jirsa & Kelso, 2000; Kelso, 1995). This means that any particular cognitive task is likely to engage (and disengage over the course of time) multiple brain regions in a task-specific fashion. In this respect, more work, both conceptual and empirical, needs to be done on a ‘theory of tasks’: which task components are shared by particular brain regions and which are unique to particular

exemplars of a given task. It may be that this effort will be facilitated by the theory of Coordination Dynamics (Haken, 1996; Kelso, 1995; Kelso et al., 2001; Kelso & Zanone, 2002), which displays certain universal properties (e.g., multiple steady states, transitions, metastability, etc.) that are common across different task realizations.

Chapter 3

Assessing recovery in middle cerebral artery stroke: A serial case study.

Results from the previous chapter showed that execution of bilateral finger-sequencing movements recruited a large network of brain areas including the M1, S1, SMA, superior and inferior parietal lobes and the cerebellum. Imagery of the same tasks, recruited the same network of brain areas (generally less active), but resulted in little activity in the cerebellum. The finger-sequencing task used in our previous study was cognitively very demanding in that it involved at least the following: planning the sequence of execution, remembering the order of movement - both temporal and spatial, monitoring movements both mentally and using sensory / proprioceptive feedback, detecting errors in the executed sequence and correcting them if necessary. The complex nature of this task per se suggested to us that task-execution involves the cooperative action of a large number of cortical and sub-cortical areas. In addition, evidence from monkey studies suggest that individual fingers do not move independent of each other and that each instructed movement is generated by the combined activation of several muscles (Schieber, 1995). This points to the possibility of the existence of a complex overlapping representation of movements in M1 and even a representation for a specific movement sequence as a whole, rather than for individual component movements. Hence the representation for implementation of a sequence of movement may be related not only to the commands

necessary to actually generate individual movements, but also to switching movements from one digit to another and the temporal ordering of the component movements in the sequence. This process presumably involves not just M1, but also other regions of the brain including the association motor cortices, the parietal cortex and even sub-cortical structures such as the cerebellum. Hence this goal-directed finger-sequencing task demands cognitive faculties more than those required for simple finger movements such as finger tapping. That motor execution and imagery share many cortical and sub-cortical mechanisms including the primary somatosensory cortex, has been shown in many previous studies (Nair et al., 2003; Jeannerod, 1994; Deiber et al., 1998; Roth et al., 1996). This observation provides clues as to why motor performance improves in individuals who mentally practice a motor task (Yáñez et al., 1998). If hemiplegic patients retain the ability to represent movements even when not being able to actually execute movements, motor imagery would provide a means of stimulating those damaged neural networks despite difficulties in producing limb movements. When stroke patients perform goal-directed action sequences (both actual execution and imagery), brain activity within these partially damaged neural regions, could provide a mechanism for functional recovery. In other words, even motor imagery could have potential therapeutic significance. Execution and imagery of the finger-sequencing task was hence considered an ideal task to understand how recruitment of different brain areas changes over time, especially when some brain areas are functionally deficient, as in stroke.

3.1. Neuroimaging of stroke

Stroke remains one of the prime causes of adult disability for a number of reasons. First, patients affected by stroke rarely achieve complete recovery. This is primarily due to the inability to reverse the ischemic process and also in part, to the failure to institute effective treatment at an early phase of the ischemic attack. A second, but related reason is the lack of understanding of the neural mechanisms that contribute to recovery of function following stroke. Third, are various contributing factors such as diet, habits, and drugs. In the past, clinical, animal and pharmacological studies have enabled researchers to identify many basic mechanisms of stroke pathology. During the last decade, several imaging techniques have been used to study stroke (Fisher et al., 1995; Bahn et al., 1996; Bakker & Pauwels, 1997; Baird & Warach, 1998; Cramer & Bastings, 2000; Davis et al., 2000). The relative merits of one modality over the other, depend on a number of factors including the time elapsed after stroke onset and the purpose of the study. For instance, DiPiero et al. (1992) used PET and Nuutinen et al. (2000) used Single Photon Emission Computed Tomography (SPECT) to study brain mechanisms during acute ischemic stroke, while Cramer et al. (1997) used fMRI to study old (months after the initial episode) stroke patients. However, the primary aim of many of these studies (DiPierro et al., 1992; Cramer et al., 1997; Nudo et al., 1996; Seitz et al., 1998; Cramer, 1999) has been to identify mechanisms of stroke recovery. One of the important findings in these studies is that ipsilateral motor pathways (in the unaffected hemisphere) assume functions that the contralateral motor pathways served prior to stroke when patients perform movement

tasks using their affected hand. This results in an increased activation in the ipsilateral sensorimotor cortex and supplementary motor area (SMA) during finger movements of the recovered hand. Cramer (1999) proposed that in patients with good recovery, the non-stroke hemisphere influences the recovering hand through trans-callosal pathways or through cortical efferents that synapse in the brainstem nuclei before descending to the spinal cord (corticoreticular pathway). Activation along the rim of the infarct was also observed during recovery from stroke (Cramer, 1999). This was mentioned as evidence for reorganization of the surviving elements along the infarct rim and expansion of the motor map in the stroke-affected hemisphere. The surviving cortical tissue along the rim also correlated with long-term outcome. Other mechanisms put forward for stroke recovery include demasking (Rijntjes & Weiller, 2002) and diaschisis (Nuutinen et al., 2000; Rijntjes & Weiller, 2002; Lin et al., 1996). Demasking refers to the process in which connections that under normal circumstances play a minor role are taxed more heavily after damage to part of the network. Diaschisis is the phenomenon in which there is decreased blood flow (hypoperfusion) and hypometabolism in an area distant from the site of infarction. Most often this occurs in the cerebellum contralateral to the cortical ischemic lesion (Lin et al., 1996; Feeney & Baron, 1986). This usually disappears a few months after stroke and hence has been used as an objective measurement for prognosis of stroke. However, Nuutinen et al. (2000) found that crossed cerebellar diaschisis (CCD) although correlated with early SPECT deficits, did not predict the functional outcome of stroke.

Both animal and human studies have reported changes in representation of the primary somatosensory (S1) and motor (M1) cortices after different manipulations such as behavioral training procedures (Jenkins et al., 1990), experimental amputation of a digit in animals (Merzenich et al., 1984), changes in afferent sensory input, repetitive cortical stimulation, pharmacological manipulation (Nudo, 1999; Sanes & Donoghue, 2000) and prolonged alteration of proprioceptive inputs (Sanes et al., 1992). It is interesting to note that functional reorganization associated with motor learning over a brief period of time has also been demonstrated in human subjects (Liepert et al., 1999; Jantzen, Steinberg & Kelso, 2002a). Thus the motor cortex seems to have the potential for rapid and large-scale functional changes in response to motor skill learning (Nudo et al., 2001 for a review). There is also evidence for specific vulnerable periods during which motor training should be instituted for better motor performance (Weiller & Rijntjes, 1999). Constraint-induced movement therapy is also known to produce significant functional improvement and plasticity in humans after chronic upper limb stroke (Levy et al., 2001). After training, subjects showed activity bordering the lesion, bilateral activation in the association motor cortices and ipsilateral activation in the primary motor cortex. In addition to constraint-induced movement therapy, performing bilateral movements has also been shown to aid recovery (Rijntjes & Weiller, 2002). Perhaps this supports Cramer's proposition (Cramer, 1999) of involvement of trans-callosal pathways in the recovery process.

Many important points may be gleaned from the results of the studies mentioned above. 1) Bilateral activation in the cortex occurs during movements of the recovered

hand, with more activation in the ipsilateral, unaffected side. 2) More activation along the rim of the infarct predicts improvement in function. 3) The initial vascular readjustments after stroke persist for weeks and settle down after a few months. 4) Physiotherapy, especially bimanual movements could help in recovery, exploiting potential trans-callosal and cortico-cortical pathways for functional reorganization of the cortex. This contributes to plasticity of the cortex and provides maximum motor output with the surviving neuronal elements.

Very few studies have however, looked at the temporal evolution of cortical reorganization in stroke patients (Lin et al., 1996; Nelles et al., 1999). In this chapter, we describe a serial fMRI case study, done on a patient with left middle cerebral artery (MCA) stroke using the same finger-sequencing paradigm as described in the previous chapter, with the aim of understanding the temporal evolution of brain reorganization during recovery from stroke and the contribution of different brain areas in the recovery process. By using unimanual and bimanual action sequences, we address the question of whether bimanual tasks and their motor / cognitive demands help improve neural reorganization. We pursued the following hypotheses: A) The affected (right) hand tasks should activate the unaffected (ipsilateral) hemisphere more than normal hand tasks during the initial sessions. If this ipsilateral activation arises due to contribution of the unaffected hemisphere towards motor function (as a compensatory mechanism), then ipsilateral activation should decrease over time when the patient shows functional improvement. B) Bimanual tasks should result in greater activation in motor areas compared to unimanual tasks C) If demasking and recruitment of several brain areas occurs during the initial period of stroke, then brain

activation should become more localized and discrete over time. D) Imagining movements should involve similar brain mechanisms and neural recruitment as actual execution and promote vascular reorganization and hence recovery.

3. 2. Materials and Methods

3.2.1. Subject

The subject, N.G. was a 65 year-old, right-handed male who suffered from a left middle cerebral artery stroke nine months before the first scanning session. Post-stroke, N.G. was undergoing regular physiotherapy without any significant improvement. Informed consent was obtained from the patient after explaining the experimental protocol to him. He was examined on three occasions – at post-stroke months 9, 11 and 12. Although recovery is believed to happen only during the initial weeks or months after the neurological insult (Heller et al., 1987; Horgan & Finn, 1997), there are several reasons for choosing a patient, nine months into the episode. Six months or later, initial vascular adjustments including luxury perfusion, altered vasoreactivity, peri-infarct edema and diaschisis should have subsided (Marshall et al., 2000).

During acute phase of stroke, there is profound mismatch between cerebral metabolism and blood flow, with varying degrees of relative or absolute hyperemia (Frackowiak & Lammertsma, 1985). Hence cerebral blood flow does not reflect the actual cerebral function during the early phase of injury. Transcranial Doppler

ultrasound studies (Akopov & Whitman, 2002; Alexandrov et al., 1999) have recently verified these changes in blood flow that occur during the early post-stroke period. The severity of hemiparesis early after stroke precludes the possibility of using motor tasks for functional brain imaging. Rehabilitative training may enhance representational plasticity and thus contribute to better functional recovery after several months (Nudo et al., 1996).

3.2.2. Physiotherapy

The patient's physiotherapy methods were based on the Feldenkrais method® (Gutman et al., 1977; Buchanan & Ulrich, 2001). He had therapy twice a week for about 8 weeks and each session lasted about 45 minutes. There were no home exercises or tasks beyond these therapeutic sessions. The effectiveness of the Feldenkrais Method lies in its potential to access the nervous system's innate processes to change and refine functioning. This method utilizes functionally based variation, innovation, and differentiation in sensorimotor activity in order to free subjects from habitual patterns and allow for new patterns of thinking, moving and feeling to emerge.

3.2.3. Physical examination and objective measurement of stroke

The first functional MRI scan was done one month after the initial physical examination results we report here. Initial examination revealed right hemiparesis with mild expressive aphasia. The patient was physically active within the impairment, was independently ambulant without any assistive devices or orthotics.

The right upper extremity was non-functional during ambulation and supporting reactions were absent. No pain was experienced during active or passive range of movements of the arm. The results of a detailed motor examination and functional profile of the right upper extremity, during the first and the last sessions are given in tables 3.1 and 3.2 respectively. Manual muscle testing was measured in grades from zero to normal. The corresponding measure in the manual muscle testing scale of 0-5 typically used in clinics is as follows. Zero - no contraction - 0/5; Trace - Palpation contraction - 1/5; Poor - Can contract the muscle in gravity minimized plane of motion - 2/5; Fair - Active movement against gravity - 3/5; Good - Active movement against moderate resistance - 4/5; Normal - Active movement against strong resistance - 5/5. No other systemic abnormalities were detected by a detailed clinical examination.

3.2.4. Task

The experiment consisted of three tasks, two unimanual and one bimanual. During the unimanual task, the subject performed movements with the right or left hand alone, whereas the bimanual task was carried out using both hands simultaneously. Each experimental task consisted of overt movement of the fingers in a prescribed sequence followed by imagery of the same task. For the latter, the subject was instructed to imagine making the requested finger sequences as quickly and as accurately as possible, and to remain relaxed without moving their fingers.

Test	A month before fMRI Session 1	fMRI Session 3 (4 months later)
Cervical Spine	Limited 30%	Limited 30%
Thoracic Spine		
Kyphosis	Severe	Severe
Thoracic cage expansion	Severely limited	Improved
Thoracic mobility	Stiff and limited	Improved
Breathing	Paradoxical	Normal
Righting reactions	Minimal	Improved
Shoulder		
External rotation	50% loss of range	35% loss
Flexion	30% loss	20% loss
Elbow and Forearm		
Flexion and Extension	Normal	Normal
Supination	40% limited	20% limited
Pronation	60% limited	30% limited
Wrist and Hand		
Wrist Flexion	Poor	Fair
Wrist Radial Deviation	Zero	Zero
Wrist Ulnar Deviation	Zero	Fair
Wrist Extension (WE)	Zero	Fair
Wrist Extension with Ulnar Deviation	Zero	Poor
Wrist Extension with Radial Deviation	Zero	Fair
Abductor Pollicis Longus/Brevis	Zero	Fair
Abductor Digiti Minimi	Zero	Poor
Adductor Pollicis	Zero	Poor
Flexor Digiti Minimi	Zero	Fair
Opponens Digiti Minimi	Zero	Fair
Opponens Pollicis	Zero	Fair
Extensor Indicis	Zero	Fair
Flexor Pollicis Longus	Poor	Fair
Flexor Pollicis Brevis	Poor	Poor
Flexor Digitorum Superficialis	Poor	Poor
Flexor Digitorum Profundus	Poor	Fair
Palmar Interossei	Zero	Fair
Lumbricals	Zero	Poor
Extensor Digitorum	Zero	Fair

Table 3-1. Comparison of results of motor examination of the patient between the first and the last sessions is shown. A general improvement in motor power can be noticed by the last session.

Functional profile of the right extremity	First session	Last session
Shoulder girdle movement without synergy	Yes	Yes
Reaching from right to left without grasping	Yes	Yes
Isolated thumb movement (flexion)	Yes	Yes
Very weak and uncoordinated grasping	Yes	Yes
Isolated finger movement in flexion	Yes	Yes
Isolated thumb/finger movement in extension	No	Yes
Hand gesturing	No	Yes/No
Close chain supporting reactions	No	No
Grasping of a small object	No	Yes
Pinch	No	Yes
Thumb and finger opposition	No	Yes
Power grip	No	No
Open and close a door	No	Yes
Open and close a car door	No	Yes
Turn an ignition key	No	Yes
Hold a tennis racquet	No	Yes
Dress independently	Yes	Yes
Catch a tennis ball with both hands	No	Yes
Button a shirt using both hands	No	Yes/No
Arm swing with gait	No	Yes/No
Writing with a pen	No	No
Using a feeding utensil with the right hand	No	Yes/No
Holding a coffee cup	No	No
Tie a shoe string	No	No
Tighten a belt	No	No
Carrying using his right forearm, if asked	Yes	Yes
Carrying using right hand	No	Yes/No
Driving holding steering wheel with left hand	Yes	Yes
Driving holding steering wheel with right hand	No	No
Swing a golf club	No	Yes
Play golf	No	Yes

Table 3-2. An examination of the functional improvement in the patient's motor control; a comparison of the first and last sessions is shown. As can be seen, a significant degree of improvement has occurred in most distal and all proximal muscles by the last session. A response marked Yes/No means that N.G. was not able to complete the task but there was observable muscle contraction in an attempt to perform the task and the response was better than that during the first session.

During the experiment, the hands were kept in a semi-prone position, by the subject's side, so that the experimenters were able to see the subject's finger movements at all times (and lack of such during imagery conditions). The fingers were labeled 1-5

from the thumb to the little finger (anatomical convention) and the sequences employed were 5342, 2435 and 4253 for left, right and bimanual conditions, respectively. Task instructions were given to the subject just before the beginning of each experimental condition. He was asked to keep his eyes closed during the entire experiment and to concentrate on the task, opposing thumb to fingers as fast, firmly and accurately as possible. One of the authors stood inside the scanner room beside the patient to monitor movement speed and precision.

3.2.5. Image acquisition protocol

The patient was scanned on three occasions (sessions 1, 2 and 3). For each session, whole brain fMRI data acquisition was carried out using a 1.5 Tesla Signa scanner (General Electric Medical Systems, Milwaukee, WI), equipped with echo planar imaging (EPI) capabilities. Images were acquired with the patient lying supine inside the scanner. Before entering the scanner, he was briefed about the tasks to be performed. The sequence of finger movements was explained to him when he was inside the scanner. Each task (unimanual and bimanual) lasted for 3 minutes, and was comprised of three periods of activation (ON, task) during which the subject performed the task and three baseline (OFF, rest) periods in which he heard only the ambient machine noise. Alternating periods of task and rest were cued to the subject through instructions to “move” and “rest” respectively, delivered through a speaker system. There were two phases - overt execution and imagery, for each task. This resulted in six conditions – execution and imagery of right, left and bimanual action sequences, respectively. Throughout the experiment, the subject’s head was supported

by a comfortable foam mold. Head movement was further minimized using foam padding and forehead restraining straps.

Scanning started with the acquisition of full head, 3D SPGR anatomical images, with the following imaging parameters: Field of view (FOV) = 26cm, frequency-phase matrix = 256 x 256, repetition time (TR) = 34ms, echo time (TE) = 5 ms, flip angle (FA) = 45°, slice thickness 2mm, and one excitation per phase encoding step. T2*-weighted gradient echo, echo planar multi-slice datasets were acquired during performance of the finger sequencing tasks. (TR = 3000ms; TE = 60 ms; FA = 90 degrees; 20 axial slices, frequency-phase matrix = 64 x 64; FOV = 24 cm; slice thickness = 5 mm and inter-slice gap = 2.5 mm). Thus the voxel size was 3.75 x 3.75 x 7.5 mm. High-resolution background images (same 20 slices, frequency-phase matrix size = 512 x 512) were also acquired for overlaying the functional data.

3.3. Data Analysis

The software packages used for data analysis were AFNI (Analysis of Functional NeuroImages, Medical College of Wisconsin; Cox, 1996) for display and analysis, and SPM (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, London) for coregistration. Preprocessing consisted of movement correction of the functional datasets using a Fourier method (Cox & Jesmanowicz, 1999), low pass filtering of the corrected time-series (cut off = 0.1 Hz) and spatial filtering of each volume using a Gaussian kernel (FWHM = 6mm). Alternating periods of baseline and movement-related activation were modeled using a boxcar

reference function shifted by 6 sec to account for the hemodynamic response delay. This delay was determined by examining the raw time series data. Regions of task-related activity were determined by cross correlation of the image time series with the reference waveform. Voxels with a correlation value (with zero time lag) less than 0.5 were masked and discarded from further analysis. The functional datasets were then coregistered to a full-head T1-weighted scan and resliced into 1mm cubic voxels (done in SPM). An activated region was defined by an individual voxel probability less than 0.01 and a minimum cluster size threshold of 630 micro liters (six original voxels) for session one and 735 μ l (seven voxels) for sessions 2 and 3. These thresholds were established based on 1000 Monte Carlo simulations demonstrating that the probability of obtaining such activation cluster for an entire volume (type I error) was less than 0.0001 (Xiong et al., 1995). Finally the functional datasets were transformed into the stereotaxic space of Talairach and Tournoux (1988).

3.3.1. ROI analysis

One of the striking observations between brain activation in this study compared to normal subjects is the general spread of activation and increase in size of clusters of activation in this stroke patient. Such a general increase in task-related activation in stroke patients relative to control subjects has been reported in several previous studies (Cramer et al., 1997; Seitz et al 1998; Chollet et al., 1991; Weiller et al., 1992). Regions of interest (ROI) were identified based on the results of previous work on normal subjects using the same finger-sequencing paradigm (Nair et al., 2003). The following 11 ROI were selected – for SMA, both hemispheres were considered

as a single ROI and the remaining 10 ROI comprised of five regions in the right and their homologous regions in the left hemisphere. These were the precentral (BA4), post central (BA3), superior parietal lobe (precuneus), inferior frontal gyrus (BA 44/45) and culmen (hand area) of the cerebellum. Voxels in each ROI, which satisfied the cluster identification criteria, were counted.

3.3.2. Comparison across sessions

To compare data across sessions, we set a correlation threshold and a cluster size for identifying significant clusters in the data from each session. Hence, clusters of brain activation that we report in this study (in all sessions) are significant according to the same statistical criterion of $p < 0.01$ (corrected). However, since our primary interest was to understand the temporal evolution of brain activation as stroke resolves, and to see how different brain regions are engaged and disengaged over time, we devised a Laterality Index (LI) to compare brain activation across sessions. For each ROI, LI was defined as the number of voxels in the left (affected) hemisphere / (voxels in the left + voxels in the right). Thus we had LI for five ROI (except SMA). This index essentially provides a better way of understanding the contribution of each brain area (ROI) to the overall task-related activation in one session and its changes over time. We also computed the mean intensity of activation of all active voxels within each region of interest.

3.4 Results

N.G. performed all tasks correctly but slowly, especially those involving the affected hand. Movement using the impaired (right) hand was especially difficult during the

first session as the motor weakness due to stroke limited finger opposition movements to execute the task correctly. However, during the second and third sessions, he was able to perform the tasks much better, as muscle power improved (see table 3.1). He reported the bimanual imagery task to be the most difficult one. No mirror movements were observed in the normal hand when N.G. performed the task using the affected hand.

3.4.1. Unimanual tasks

During task execution using the unimpaired hand (left-move) and while imagining the same movements (left-image), there was more contralateral than ipsilateral cortical activation, as revealed by the Laterality Index (LI) (always less than 0.5 in any brain area for all sessions). This is the expected pattern of brain activation for such motor tasks in normal subjects (Nair et al., 2003). A similar pattern of activation (contralateral > ipsilateral) was observed in the sensorimotor cortex (SMC) for the right-handed execution (right-move) task too. Fig 3.1 shows brain activation in an axial slice ($Z = 50$ of the Talairach atlas) during the right-handed execution task across sessions. It can be seen that activation in the contralateral (left) SMC is greater than that of the ipsilateral (right) side in all three sessions. However, activation in the precuneus (superior parietal lobe) exhibited the opposite pattern – ipsilateral (right) > contralateral.

Fig.3.1 also illustrates a general decrease in the spread of activation over sessions; i.e., compared to the first session, brain activation became more localized by the third session. Interestingly, the LI values during the right-handed execution task in M1,

showed an increase over sessions (0.58, 0.65, 0.82 in sessions I, II and III respectively). It should be noted that in right-handed tasks, LI depicts the contribution of the contralateral (left) hemisphere towards total activation (left + right) and 1 minus LI (denoted 1-LI, in future), that of the ipsilateral hemisphere. Hence an increase in LI during the right-handed execution task over sessions suggests greater contribution of the left hemisphere and a progressive decrease in the contribution of the right (ipsilateral) M1 to total activation (left + right). A similar decrease in activation over sessions was also observed in the Supplementary Motor Area (SMA) (fig.3.1). The right-handed imagery task (right-image) resulted in a pattern of cortical activation very similar to that of the right-handed execution task across sessions, but almost always with less intensity of activation in bilateral M1 (Table 3.3 – part A).

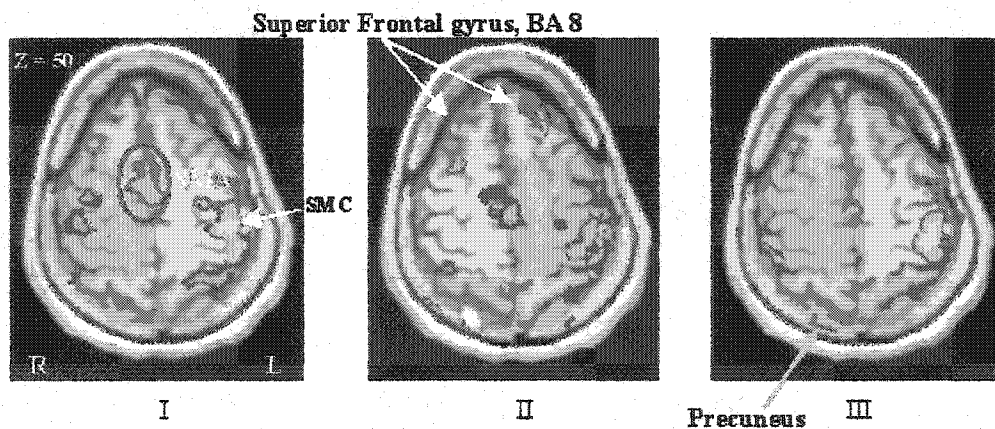


Fig.3.1. - Comparison of brain activation during right-move task (bad hand) across sessions I, II and III. SMC – Sensorimotor Cortex; SMA – Supplementary Motor Area; Z = 50 indicates the inferior-superior coordinate of the axial slice in the Talairach atlas. In all sessions, contralateral (left) sensorimotor cortex shows stronger activation than ipsilateral (right). SMA activation decreases with session; Precuneus (green arrow) activity increases during the last two sessions, when compared to the first. Activity is more diffuse in the first session and an overall decrease in the spread of neural activation is seen over sessions.

Part A		Session I	Session II	Session III
Intensity of activation in Right M1:				
	Right-Move	0.69	0.68	0.68
	Right-Image	0.53	0.68	0.41
Intensity of activation in Left M1				
	Right-Move	1.2	0.84	0.98
	Right-Image	0.61	1.00	0.87
Part B				
Ipsilateral Precuneus activation				
	Right-Move (1-LI)	0.48	0.61	0.96
	Left-Move (LI)	0.17	0.41	0.39
Part C				
Intensity of activation in ipsilateral Precuneus				
	Right-Move	0.63	1.14	0.9
	Left-Move	0.61	0.76	0.63
	Right-Image	0.46	0.57	0.83
	Left-Image	0	0.45	0.25
Part D				
Laterality Index (LI) in M1				
	Right-Image	0.42	0.53	0.49
	Bimanual-Image	0.46	0.54	0.72

Table 3.3. Intensity of activation and laterality indices in the stroke patient over time in several tasks

Recruitment of precuneus (superior parietal lobe) occurred in a different manner than sensorimotor cortex during left-move and right-move tasks and their imagery counterparts. As can be seen in fig.3.1, more ipsilateral than contralateral precuneus activation was evident during the right-move task during all sessions. In fact, when the contribution of the ipsilateral precuneus (1-LI) was compared with that of ipsilateral M1 during the right-handed execution task, an inverse relationship was observed ($r = -0.99$) (see fig. 3.2).

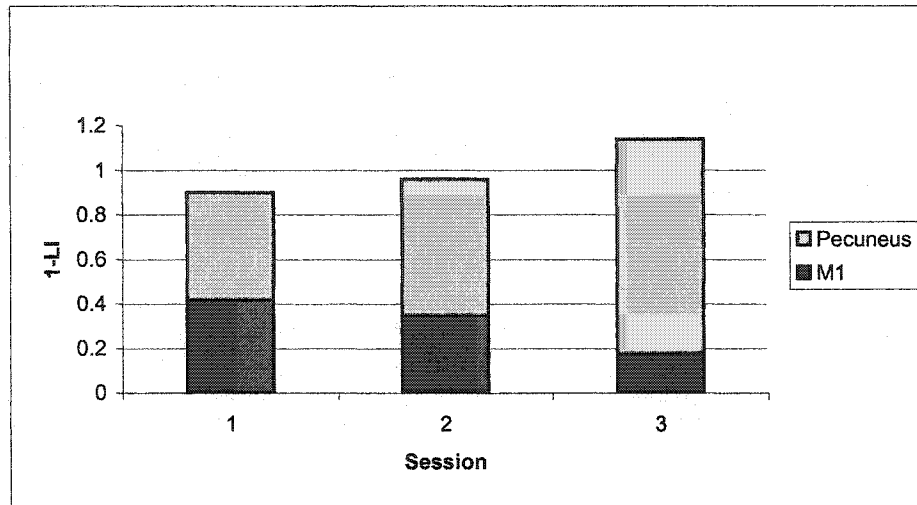


Fig.3.2. Contribution of ipsilateral M1 and superior parietal lobe (Precuneus) as shown by 1-LI values, to their corresponding total activation (left + right hemisphere) during the right-handed execution task. M1 activation decreases while activity in the Precuneus increases with session. A negative correlation ($r = -0.99$) was observed between these two activations over time.

Interestingly, a larger cluster of activation in the ipsilateral precuneus was found when N.G. executed the task using the affected hand (right) compared to the good (left) hand (as indicated by 1-LI of right move greater than LI of left-move – see Table 3.3 – part B). Comparing the intensity of activation in precuneus, we also noted that executing and imagining sequences using the affected (right) hand resulted in stronger ipsilateral activation than while using the good (left) hand (Table 3.3 – part C). An increase in fMRI signal occurred in the inferior frontal gyrus (BA 44/45) including the peri-infarct region during the right-move task, but no specific pattern of change could be observed over sessions. In all sessions, when the subject performed the task using the affected (right) hand, more voxels were active in the contralateral (left) cerebellum than the ipsilateral. However for the left move task, more ipsilateral

cerebellar activation consistent with the normal pattern was observed (data not shown).

3.4.2. *Bimanual tasks*

Performing the bimanual tasks recruited several brain areas in both hemispheres. In normal subjects the contribution of different brain areas to the entire activation pattern does not change across sessions. However, in our stroke patient, who was on treatment and was functionally improving, the extent to which different brain areas are recruited over time may change depending on the degree of recovery in these areas. Hence, rather than comparing LI of bimanual tasks across sessions, we were more interested in comparing the LI of the right-move task in each session with that of the bimanual-move task of the same session. This yields more useful information as the basic vascular changes consequent to functional improvement remain the same for all tasks (unimanual and bimanual) in one session, and the contribution of different brain areas in each hemisphere (during right-move and bimanual-move tasks) is almost entirely due to the difference in the task demands; i.e., we are able to assess how much of the difference in brain activation in the side of the lesion is due to a change in task from unimanual to bimanual alone. In other words, this helps us understand whether the bimanual task facilitates reorganization of blood flow in the side of the lesion and whether that helps recovery. When we compared the LI in primary sensorimotor cortex during right move and bimanual move tasks, no increase for the bimanual task was observed (no increased activation in the left side). However, the value of LI was always greater than 0.5 in right move and bimanual

move tasks, indicating that more voxels were active in the sensorimotor cortex of the left side (side with the lesion) than the right. Both during right-move and bimanual-move tasks, M1 of affected side (left) showed higher intensity activation than the right side (fig.3.3 – gray > dark during right-move and dotted > stripes during bimanual-move). Also during the second and third sessions, bimanual execution of the task resulted in increased intensity of activation in the left M1 compared to right-handed execution (fig.3.3 – compare dotted and gray bars). Between right-image and bimanual-image, laterality index in M1 showed an increase during bimanual-image in all sessions (Table 3.3 – part D). This suggests that the bimanual task recruits more voxels in the damaged hemisphere than the unimanual task.

Brain activation during bimanual execution and imagery tasks is shown in fig 3.4. A decrease in the spread of activation by the third session is evident both during bimanual execution and imagery (row 1 indicates activation in the first session and row 2 that in the second). It is interesting to note that execution and imagery result in quite similar patterns of activity across sessions.

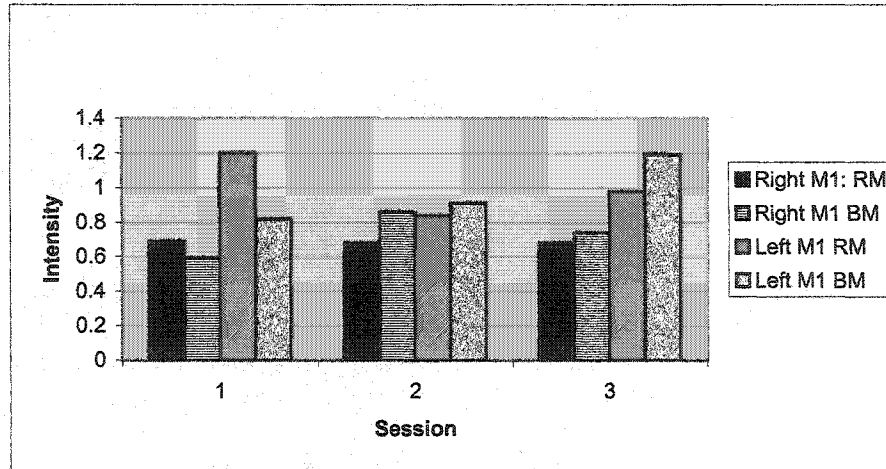


Fig.3.3. Intensity of activation in primary motor cortex (M1, Brodmann's area 4) during the right-handed and bimanual overt execution tasks. Although in the first session more intensity of activation is seen in the right-handed than the bimanual task in both hemispheres, this pattern reverses in sessions 2 and 3 (compare dark and striped bars; and gray and dotted bars). A higher intensity of activation was observed in the lesion hemisphere (left) than the right hemisphere, both during the right-handed and bimanual execution tasks (gray > dark and dotted > striped). RM – Right-Move; BM – Bimanual-Move.

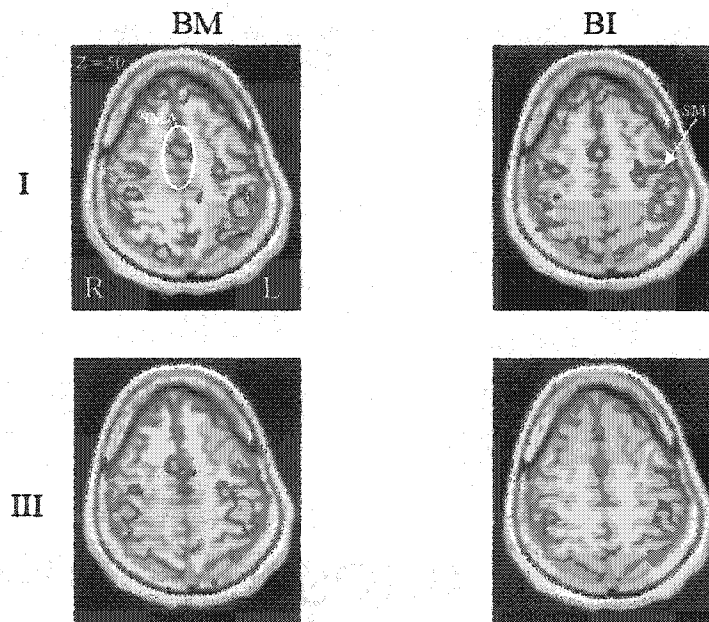


Fig 3.4. Comparison of brain activation during bimanual-move (left column) and bimanual-image (right column) tasks in the first and last sessions (first and second row respectively) shows that the primary sensori-motor cortex (SMC) of the lesion side (left, L) is more active during both tasks and across sessions. A general decrease in the spread of activation and decreased activity in the supplementary motor area (SMA) by the third session is also seen.

3.5. Discussion

Given the complexity of voluntary movement, both in terms of the selective engagement of neuroanatomical structures in time and the vast repertoire of behaviors possible, it is reasonable to assume that an intricate network of cortical and subcortical structures is involved, especially in fine movements such as finger sequencing. This spatiotemporal sequencing task resulted in brain activations that isolated the dimensions of handedness (left and right), manual engagement (unimanual and bimanual) and cognitive influences (imagined and executed) on action. Our data suggest that execution and imagery of finger sequences using the affected hand and using both hands had pronounced effects on recruitment of neural areas over time and hence quite likely on neural reorganization during recovery.

Previous research has shown that motor recovery from stroke is in part the result of the extension of motor areas in the affected hemisphere and the recruitment of ipsilateral motor pathways. But what exactly does the non-stroke hemisphere do and how does it contribute to recovery? One possibility is that when brain regions in one hemisphere suffer damage due to stroke, the other hemisphere is recruited more to compensate for the loss of function. This is consistent with animal studies that demonstrated expansion of neural elements in the non-injured, ipsilateral hemisphere in animals recovering from a unilateral lesion (Jones & Schallert, 1994; Kozlowski et al., 1996). An increase in both dendritic branching (Jones & Schallert, 1992) and synaptic number (Jones et al., 1992; Stroemer et al., 1995) has been noticed in both the stroke-affected and unaffected hemispheres days after the lesion. It is also

possible that the non-stroke hemisphere is responding to an increase in perceived task complexity. Several researchers have shown that bilateral brain activation occurs with an increase in task complexity in normal subjects (Rao et al., 1993; Shibasaki et al., 1993). Suppression of unwanted movements may well be another role of the non-stroke hemisphere. It is possible that the above-mentioned factors separately or in combination are responsible for recruiting the undamaged hemisphere. However, the exact pathway through which ipsilateral M1 exerts control is not known. Transcranial magnetic stimulation (TMS) of the normal, ipsilateral M1 in stroke patients with good recovery, failed to elicit a robust response in the affected hand (Turton et al., 1996; Netz et al., 1997). Since TMS affects only mono to oligosynaptic pathways, Cramer (Cramer et al., 1997; Cramer 1999; Cramer, 2000) posited that it is unlikely that this control (by ipsilateral M1) occurs through the undecussated corticospinal fibers, since this pathway is monosynaptic. Instead it was suggested that recovery possibly occurs through polysynaptic pathways such as trans-callosal and corticoreticular pathways. Following these results, it is reasonable to surmise that more ipsilateral activation is expected during the initial session when the patient had maximum functional deficits and ipsilateral activation decreases as the patient recovers from stroke. A decrease in ipsilateral M1 activation and a corresponding increase in contralateral activation over time, when the subject performs the task using the impaired hand as seen in this stroke patient, suggest that the additional compensatory activation seen in the ipsilateral M1 during the initial session is not essential in later sessions. Greater activation in the contralateral (lesion) hemisphere over time indicates that more neural elements become functional in later sessions and are recruited for task

execution. This may well be one of the signatures of functional improvement, as it conforms to the pattern of activation we see in normal subjects when they perform finger-sequencing tasks using their preferred hand.

Increased reliance on brain structures normally involved in motor control may be an integral part of reorganization of motor systems and may be responsible for the widely distributed regions of neural activation seen in the first session (Marshall et al., 2000; Calautti et al., 2001; Ward et al., 2003). In our patient, as his motor power and dexterity improved over sessions by rehabilitative therapy, the distributed neural activation pattern changed to a discrete and more localized pattern of activation. Several previous studies have reported greater and widespread brain activation in early, compared to the later stages of stroke (Marshall et al., 2000; Calautti et al., 2001). An initial increase in dendritic branching, number of synapses and hyperexcitability has been suggested as being responsible for this general spread of activation. However, Buchkremer-Ratzmann et al. (1996) reported in rodent studies that over time, this increase is followed by a pruning back of neurons and a decrease in hyperexcitability. With improvement in function of the stroke affected neural areas, these mechanisms could contribute to a reversal of the initial demasking that was observed in our patient. One should however, be careful in attributing these observations to functional improvement from stroke, as it is possible that a decrease in recruitment of neural resources, specifically ipsilateral motor regions, and an increase in activation of contralateral M1 over sessions could reflect the neural correlates of learning (Nudo et al, 1996; Karni et al., 1995; Ungerleider et al., 2002).

In other words, as the subject improved, the task became easier to perform resulting in a lesser degree of activation in the involved brain regions. Karni et al. (1995) demonstrated that M1 activation evoked by trained finger sequences although was significantly larger than that due to the untrained ones, activation did not extend beyond the hand representation area itself. This means that learning a motor sequence induced more activation of the subpopulation of voxels in the hand area that showed significant response to performance of the trained sequence. Since our experimental sessions were separated by a month each, with no practice sessions in between, motor learning if any, is more likely to have occurred within a session than across sessions. Moreover, the finger sequence for each task, unimanual and bimanual, was different and it was quite difficult for the subject to have learned all three sequences within the duration of the experiment (18 min for execution and imagery together). No obvious change in movement parameters (such as improvement in speed or accuracy, as confirmed visually) suggestive of learning was observed. Moreover, compared to other forms of memory such as episodic memory, changes in performance are known to evolve slowly, requiring many repetitions over several training sessions (Karni, 1996). Hence changes in neural activation in this case most likely reflect neural correlates of functional recovery from stroke.

In both execution and imagery tasks, our subject had his eyes closed and hence had to rely on knowledge of the spatial dimensions of the task along with the sensory feedback experienced during movement. Accessing this memorized spatial information may have contributed primarily to the parietal lobe activation observed

during execution and imagery. However, it is unusual for ipsilateral activation to be larger than contralateral activation, especially when right-handed individuals perform the task using their preferred hand. In our subject, even when the pattern of blood flow to the left sensorimotor cortex had been restored closer to normal in later sessions (as evidenced by LI values in the left sensorimotor cortex greater than 0.5 and increasing over sessions during the right-move task), blood flow to ipsilateral (right) parietal cortex appeared to increase during the right-move task. These observations suggest ongoing vascular readjustments and vicariousness of function in the parietal cortex of this patient. Reciprocal activation of M1 and superior parietal lobule over time during the right-handed execution task demonstrates a major role of the connections between these two regions in the process of recovery. Recent imaging studies have verified the functional connectivity of such pathways during motor tasks in the human brain in vivo (Guye et al., 2003). Data tend to indicate that the undamaged parietal cortex (right) takes over the function of the affected side even when the left sensorimotor cortices are normal, to help maintain optimal motor performance. Parietal cortex (especially the superior parietal lobule, Brodmann's area 7, the precuneus) is engaged especially for action sequences that rely on remembering and executing the correct ordering of task components along with processing the sensory consequences of action. Using motor imagery, Johnson (2000) demonstrated in early hemiplegic patients that they retained the ability to accurately represent movements of both their healthy and paralyzed limbs. These patients could use motor imagery to activate damaged motor networks, except when the lesion involved the right posterior parietal and left frontal areas. This highlights the role of parietal cortex

in representation of movements and also as a key element of functional reorganization during recovery from stroke.

The neural tissue around the core of the infarct (also called penumbra) contains viable tissue that helps recovery and the volume of surviving peri-infarct penumbra correlates with the degree of neurological recovery (Furlan et al., 1996). It has been shown that an increase in many growth-related proteins occurs in this region of intact cortex around the infarct (Li et al., 1998). Primate studies have also suggested that the surviving peri-infarct neural elements may contribute to recovery by providing a substrate for reorganization of cortical representational maps. Hence, an increase in blood flow to the peri-infarct area is desirable and could be considered evidence for functional reorganization of the viable tissue around the infarct. Our data did not provide clear evidence for this.

Bimanual tasks are different from unimanual tasks in several ways. First, they are much more difficult than unimanual tasks. Performing finger sequences using both hands is by itself a very demanding task, which places large demands on neural networks subserving temporal and spatial memory. Second, proper execution and imagery of this task requires more attentional resources. Hence bimanual tasks recruit a larger network of brain areas for task execution. Since brain areas in both hemispheres are involved, this task serves to improve functions of the affected hemisphere through cortico-cortical and trans-callosal connections and also facilitate functional connections to surviving neural elements around the infarcted region. As

observed in animal studies, it may be that through these bihemispheric connections, there is a reduction in GABA receptors or bilateral increases in glutamate NMDA receptors (Qu et al., 1998) in areas functionally connected to the infarcted region. These in turn act to unmask latent horizontal connections and aid in functional recovery (Jacobs & Donoghue, 1991; Rioult-Pedotti et al., 1998). The existence of these horizontal connections throughout M1 has been verified by Donoghue and his colleagues (Hess & Donoghue 1996; Sanes & Donoghue, 2000) using intracellular recordings and field potential recordings of in-vitro preparations. Jacobs and Donoghue (1991) also showed that local blockade of GABAergic inhibition in one part of M1 unmasks existing horizontal connections that then reveal hidden representations of limb movements in other parts of M1. Our data revealed stronger M1 activation in the lesion hemisphere both during bimanual execution and imagery tasks. This observation along with the superior parietal lobe activation observed during bimanual tasks, support our proposition that bimanual tasks aid in neural reorganization and functional recovery from stroke. In this process, several brain areas including, but not limited to the primary sensorimotor cortex, superior parietal lobule, SMA, and cerebellum are involved. It is interesting to note that bimanual imagery tasks also result in similar activation patterns as overt execution. This observation warrants attention as it opens the possibility of using imagery as a potential therapeutic / rehabilitative tool for functional improvement while recovering from stroke.

SMA is known to be involved in motor planning and execution of difficult tasks (Nair et al., 2003; Shibasaki et al., 1993). Activation in SMA decreased over time in our stroke patient during task execution with the affected (right) hand, although previous work (Cramer, 1999) has found evidence for a progressive increase in the volume of SMA activation during movements using the recovering hand. This decrease may reflect a decrease in perceived complexity (lesser motor planning / execution demands) of the task. Alternately this may also suggest a recovery process wherein there is increased reliance during the early post-stroke period on motor areas (SMA, premotor cortex) whose efferent tracts descend in parallel with those originating in M1 (Fries et al., 1993). The initial dependence on these pathways seems to decrease as the subject recovers.

As previously mentioned, a decrease in activation of the cerebellum contralateral to the cortical lesion (here right cerebellum consequent to a left-sided cortical infarct) is known as crossed cerebellar diaschisis (CCD). Our study revealed diminished activity (as revealed by the number of voxels) in the right cerebellum for task execution with the affected hand (right-move) and greater activity in the left cerebellum during left-move task. If this difference in ipsilateral activation as revealed by fMRI BOLD response could be considered equivalent to blood flow and metabolism measurements of PET and SPECT, then there is evidence for crossed cerebellar diaschisis in this patient even nine months after stroke. Persistence of cerebellar diaschisis does not necessarily indicate a bad prognosis (Nuutinen et al., 2000) and CCD has been demonstrated in many conditions such as supratentorial stroke, frontal tumors (Otte et al., 1998), following intracarotid amytal injection (Kurthen et al., 1990), and

refractory seizures (Mewasingh et al., 2002). One of the mechanisms suggested is disconnection of glutamatergic corticopontocerebellar tracts as a result of the neurologic insult. Diaschisis is known to resolve by itself although the exact duration and mechanisms still remain unclear. It is possible that some of the corticopontocerebellar fibers were affected in this patient with a large cortical area affected by stroke. This conjecture is supported by Miura et al. (1994) who found that in patients with MCA stroke involving frontal sensorimotor cortex, CCD persisted for up to 5 years after the onset of stroke. Our patient was clinically recovering from stroke regardless of the presence of CCD. Whether this would resolve over time cannot be predicted using our neuroimaging results at this time.

One of the important findings of this study is that chronic patients (months after the neurological insult) still maintain the ability to recover and be functionally independent. The success of the therapy program depends on identifying strategies a) to trigger the motor pathways that lie dormant in these patients due to limb disuse and neglect b) to enhance the cross talk between brain areas within and across hemispheres. Our work supports the idea that motor imagery and bimanual movements of complex finger sequences are useful in this regard. It is interesting to see that the Feldenkrais method® has been able to activate the dormant motor pathways successfully in this patient. We also saw how his functional improvement related to recruitment of different brain areas into the motor network over time. However, we caution readers to the fact that these results pertain to one subject only and similar studies in a larger population of patients are necessary to study the

applicability of such treatment protocols in different types of stroke and motor disabilities.

3.6. Summary and Conclusions

This serial functional imaging study in a patient suffering from left MCA stroke revealed the temporal evolution of brain activation over a period of three months, as the patient was recovering from stroke. A large network of brain areas including the primary motor cortex (M1), parietal cortex, SMA and the cerebellum was involved in recovery. Performing the task with the affected hand involved ipsilateral sensorimotor cortex more during the initial session, but activity decreased over time. BOLD response in the contralateral (left) sensorimotor cortex increased over time, pointing to the recruitment of more neural elements in the lesion side. The unaffected (right) superior parietal lobe became more active over time and possibly took over the function of the affected side to optimize performance of the task. The above observations provide evidence for the cooperative action of several cortical regions within and even across hemispheres, to help recover from the neurological insult. The coupling and decoupling of different brain areas into the functional motor network over time also suggest that proper rehabilitative techniques trigger the inherent plasticity of the network to achieve better motor output, even months after the ischemic episode. In addition, the widespread neural activation observed in earlier sessions changed to a more localized pattern of activation suggesting that fewer brain areas was sufficient to carry out the task as the subject recovered. Bimanual tasks seemed to help the recovery process by recruiting more voxels in the lesion

hemisphere. One of the important results of this study is that imagery of movements also resulted in similar brain activation as actual execution. Using imagery tasks we provided evidence at the neural level, that hemiplegic patients retained the ability to activate neural pathways that are normally involved in executing goal-directed action sequences, despite the loss of ability to actually execute movements. Imagery tasks activated these damaged motor networks and contributed to functional recovery and hence could potentially be used as a rehabilitative tool. Our study also highlights the fact that imaging techniques such as functional MRI could be used to identify neural reorganization during recovery from stroke.

Chapter 4

Limbic responses while listening to music: Effects of performance expression and musical training

4.1 INTRODUCTION

Music performance involves sequential action and cognitive/motor planning. The observation that rhythmic stimuli and music can help people achieve better movement coordination may arise out of the motivational component of music. We all know that listening to music involves aesthetic and affective experiences. It is possible that brain regions responsible for these experiences modulate motor activity in specific ways. To understand this process better, it is essential that we identify activity in brain regions corresponding to affective experiences while to music performance. One of the fundamental issues in music is whether we can identify specific features of music that give rise to such affective experiences. Using functional MRI, can we detect neural responses related to this affective experience, such as activation in the limbic and paralimbic areas when subjects listen to music? To what extent are any such responses dependent on musical training? These are the questions that we address in this chapter.

Previous research has investigated affective responses to music. Krumhansl (1997) observed that sad music resulted in increased systolic, diastolic and mean arterial pressures and decreased heart rate, skin conductance and finger temperature. Sloboda

(1991) linked certain structural properties of music to specific physiological responses – for instance, it was shown melodic appoggiaturas evoked tears and relatively sudden changes in harmonies evoked shivers. Although affective physiological responses to music have been documented, little is known about what features of music or music performance give rise to such experiences. Moreover, only a few studies have examined the neural mechanisms of these affective responses and none used functional MRI. Recently, Blood & Zatorre (2001) examined the neural mechanisms underlying emotional responses to music using Positron Emission Tomography (PET). As the intensity of the subjects' pleasurable experience (chills) increased, more neural activation was observed in brain regions thought to be involved in reward/motivation, emotion and arousal, including the limbic areas and ventral medial prefrontal cortex. In another PET study, Blood et al. (1999) showed that when subjects listened to music-like passages which varied systematically in the degree of sensory dissonance, cerebral blood flow changes in the right parahippocampal gyrus and precuneus regions correlated with increasing dissonance while activity in the orbitofrontal, subcallosal cingulate and the frontal polar cortex correlated with decreasing dissonance. The brain regions observed in these two studies were distinct from the areas involved in the analysis of structural components of music such as pitch, timbre and rhythm. Evidence for the existence of separate neural pathways for emotional interpretation compared to structural interpretation of music also comes from a previous case study (Peretz et al., 1998) of a patient with damage to bilateral temporal lobes and the right frontal lobe following surgery. She suffered from amusia (but without aphasia) and mainly music agnosia (cannot

discriminate nor identify melodies, cannot learn new melodies). Nevertheless, this patient exhibited normal emotional judgment for a piece of music despite the loss of several music processing abilities. The neural correlates of music processing have been studied widely in the past decade and researchers have successfully identified brain areas involved in the judgments of pitch, contour, rhythm, meter and other structural aspects of music (Zatorre et al., 1994, Liegeois-Chauvel et al., 1998, Platel et al., 1997; Tillman, Janata, & Bharucha, 2003; Janata et al., 2002; Levitin & Menon, 2003). However, the issue of musical communication remains open.

The psychological study of emotional communication in music has focused to a large extent on the issue of communication accuracy (Juslin, 2001). In this approach, performers are asked to record short musical excerpts in a way that will convey basic emotions, such as anger, fear, joy, and the like. Listeners then attempt to name the basic emotion that the performance was intended to convey. It has been shown that listeners, whether musically trained or not, are in general able to name the emotion that a musical excerpt intends to convey, even across cultures (Balkwill & Thompson, 1999). Moreover, listener ratings can be predicted based on basic musical features including tempo, articulation, intensity, and timbre (see Juslin, 2001 for a review).

However, there are problems associated with study of communication of emotion in music performance. First, because music flows through time, it is difficult to pinpoint musical processes that evoke particular affective responses. Many theories of musical aesthetics emphasize that music does not represent basic, categorical emotions

(Meyer, 1956; Raffman, 1992; Langer, 1951). As Kraut (1992) observes, "... listeners rarely experience joy, jealousy, indignation, envy, love, or other stereotypical emotions in response to uptempo Ornette Coleman performances." Rather, music communicates a *dynamic* form of emotion, a form of emotionality that has been linked to Stern's (1985) theory of *vitality affects* (Sloboda & Juslin, 2001). Vitality affects refer to qualities related to shape, contour, intensity, and movement – characteristics best described in dynamic terms. Stern (1985) argued that vitality affects are important in early communicative acts of mother and infant, who respond to one another by adjusting the intensity, timing and contour of their expressive acts. Quite similar to how we modulate our voice for communication of meaning in speech, music performers use various cues collectively called performance expression, to convey emotion and meaning to listeners. This is discussed further in the next paragraph. Second, listeners often cannot describe their experiences in words (called ineffability; Raffman, 1992) that it is difficult to precisely know what they felt. Third, experiments and explicit instructions given to subjects impact so much on the listening process that the task destroys the very thing it is supposed to measure - the problem of reactivity (Neale & Liebert, 1986). To get around subjective measures such as verbal descriptions of feelings and emotional rating scales and to look at the brain directly for evidence of aesthetic and affective experiences while listening to music, we decided to use fMRI in this study. Finally, previous studies examined emotion in music using short excerpts of music lasting a few seconds. We want to simulate the process of listening to music and hence use the whole piece of music.

In piano performance, the cues performers use to convey meaning in music are limited mainly to fast time-scale fluctuations in timing (rubato and articulation) and intensity (dynamics). The ways in which performance timing and intensity variations communicate musical structure (e.g. phrasing, meter) has been extensively studied (Palmer, 1997; Repp 1998b; 1999a; b; c; d, Schaffer & Todd, 1987) and has even been modeled in some detail (Large & Palmer, 2002).

Repp, in a series of articles studied the expressive cues performers use in music performance and how these affected listeners' perception and aesthetic outcome. He used the Etude in E major, Opus 10, No. 3, by Frederick Chopin as the stimulus, since performers typically employ a wide range of intensity and tempo fluctuations in order to render it aesthetically appealing. Using the initial few bars of several commercially recorded performances of this musical piece, Repp studied how performers manipulated timing (1998b), dynamics (1999a) and how these contributed to the aesthetic outcome in listeners (1999b). Repp (1999b) noted that the aesthetic impression relied on factors such as texture and tone, in addition to changes in intensity and dynamics, and that different patterns of timing and dynamics are aesthetically acceptable for the same music. In fact, he also found that majority of the performances exhibited a typical timing profile which when applied to the music score rendered an "average" performance that was aesthetically pleasing to listeners (Repp, 1997). Since a great deal of research has been done using this Etude by Chopin and much is known about how the structural characteristics and variations thereof contribute to listeners' perception of affect, we decided to use the same musical piece as our stimulus. In this study, we use only the two versions at both ends

of the expressive continuum to look for limbic / paralimbic activation. Based on our knowledge of how expressive cues communicate affect in music, we hypothesize that the expressive version will result in limbic activity while the mechanical will not.

One of the outstanding questions that we address in this study is whether musical training affects perception in specific ways and hence the limbic brain responses. The motor and cognitive demands of musical training are known to result in structural adaptations in the brain including changes in representation of motor maps. Specific functional and structural changes have been observed in regions such as the planum temporale, especially in musicians with absolute pitch (Ohnishi et al., 2001; Keenan et al., 2001; Schlaug, 2001), corpus callosum (Lee et al., 2003) and the cerebellum (Hutchinson et al., 2003). We also know that musicians are trained to learn the skills of music performance and are adept at independently controlling performance cues such as expressive timing and dynamics in order to give an expressive shape to the melody. They recognize the use of these cues much better than non-musicians. However, using the same piece of music, Repp previously has shown in non-musicians that (IOI) increment in mechanically timed music is more difficult to detect where expressive lengthening typically occurs in artistic performance (1998a). This result suggested that even subjects without formal musical training expected temporal deviations in musical performance and were successful in decoding the cues for performance expression. Nevertheless, this result does not necessarily rule out the possibility of differential brain recruitment in musicians and non-musicians while listening to music performance.

We report two experiments using functional Magnetic Resonance Imaging (fMRI). Our participants listened to two versions of the same composition, one performed by a highly trained musician, and the other generated by a computer to conform as precisely as possible to the notated composition. Because the two stimuli were the same musical piece as defined by the musical notation, they shared all the basic features generally associated with music: pitch, melody, harmony, rhythm, grouping, meter, (mean) tempo, and architectonic structure. The two pieces differed only in those features associated with performance expression, which consist of local changes in timing and intensity - dynamics, articulation and rubato. The differences in brain activation while listening to the two versions of music index the neural processes associated with the perception of musical expression, but not with any features the two performances had in common. We address the following questions. Can expressive cues in the performance result in limbic activity? Do musical training & skill affect the way one listens to music? Can we draw inferences from our observations about how musical performance conveys emotion and meaning?

4.2 EXPERIMENT 1 - Methods

4.2.1. Stimuli

The stimuli were two digital recordings of a single piece from the classical repertoire, Etude in E major, Opus 10, No. 3, by Frederick Chopin. The first recording, the *expressive performance*, was a performance of the piece by an advanced music student (senior piano performance major at Harrod Conservatory, 20 years musical training). The piece was performed on a Kawai CA 950 digital piano, and recorded

via MIDI into Studio Vision running on a Macintosh G3 computer (Mac OS 9.0.4). The performance was divided into six 30-45 second listening blocks, to conform to the block design of the functional MRI paradigm. Blocks were chosen to correspond to musical sections or subsections, to cause minimal interruption to the natural flow of the music.

The second recording, the *mechanical performance*, was synthesized on the computer by changing the onset time and duration of each note of the expressive performance to precisely match that of the musical notation. The MIDI onset velocity (linearly related to sound level) of each note was set to 64 (an intermediate value), and pedal information was eliminated. The mechanical version was then divided into listening blocks, and each block was matched for mean tempo with the corresponding block of the expressive performance by time stretching/compression of the MIDI data. Listening blocks were interspersed with 30-second blocks of silence. Figure 4.1 presents the piano roll notation of the MIDI recording of the expressive performance (upper panel), along with local changes in performance tempo (lower panel). Piano roll notation is an idealized spectrogram of the performance, in which pitch (n.b. not frequency) is given as a function of time; this is enabled due to MIDI recording, which also provides precise onset and offset times ($\pm 1ms$) for each note. Each rectangle thus corresponds to a single note of the performance. The main degree of freedom that pianists control in this type of performance is local tempo (Fig 4.1 – lower panel); performers speed up and slow down as the performance progresses, and these tendencies have been linked to performers' musical interpretation of a composition (Palmer, 1997; Repp, 1998b; 1999 a;b;c).

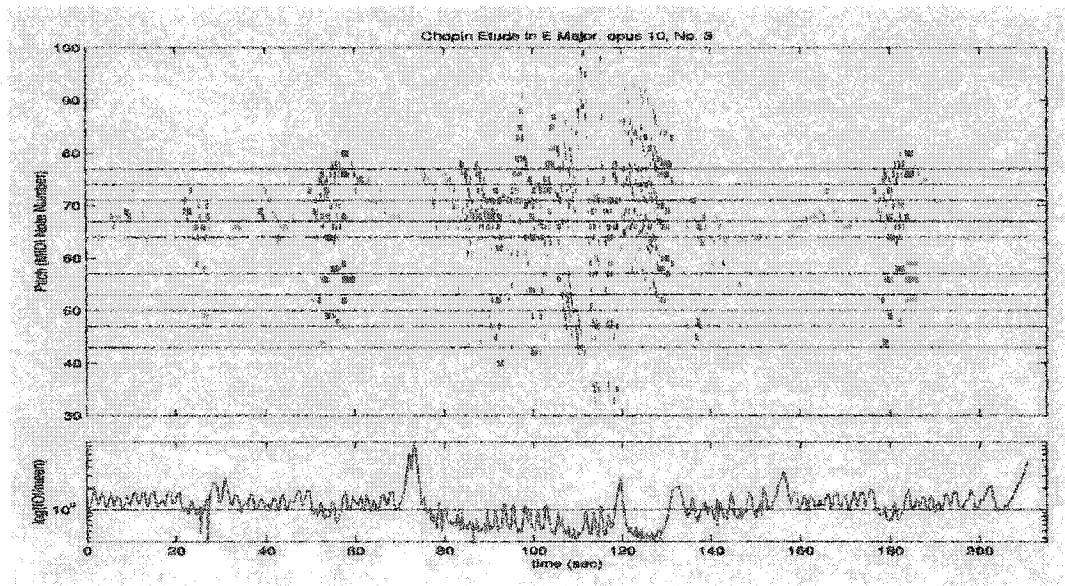


Fig 4.1. Piano roll notation of Chopin Etude in E Major, opus 10, No 3. The upper panel shows onset velocity of each note (intensity) in color (yellow-red). The lower panel shows fluctuations in tempo during the performance. The horizontal line in the lower panel indicates the mean tempo.

Performers also control the onset velocity of each note (related to intensity), shown in the upper panel as color (yellow – red). An additional degree of freedom relating to performance timing is articulation, including note duration, and use of the sustain pedal. The lengths of the individual rectangles represent the duration of notes of the performance (fig 4.1 – upper panel). Both stimuli were played back via MIDI, through the Kawai CA 950, and recorded on a Sony PCM 2500B digital tape recorder, for presentation to our participants.

4.2.2. Equipment

Images were acquired using a 1.5T Signa scanner (General Electric Medical Systems, Milwaukee, USA). The stimulus was played to the subjects from the digital tape

through non-magnetic tubes and headphones (Avotec Inc., Stuart, Florida). Headphones were custom-modified to deliver sound directly into the external auditory canal, by attaching soft-tipped earplugs of a Littmann™ Cardiology III stethoscope to a thick plastic tube that was shaped to precisely match the shape of the stethoscope, and then inserted into the sound-protective Avotec headphone shells. Sound barriers (Sonex™, 1 inch thick, mean 30 dB attenuation within the frequency range of our performance) were used to insulate the auditory junction box and the head coil of the magnet from scanner noise.

4.2.3. Participants

Four right-handed subjects, three males and one female, participated in this experiment. All participants were musicians (performance experience: mean 31.5 years, range 25-40 yrs), and all reported normal hearing. All participants gave informed consent prior to the experiment, and the protocol was approved by the Institutional Review Board at Florida Atlantic University.

4.2.4. Stimulus Presentation

Each condition (*expressive* and *mechanical*) lasted for 6 minutes and 33 seconds, and was comprised of 6 periods of activation (ON, listen, 30-45 sec) during which subjects listened to music and 6 baseline (OFF, rest, 30 sec) periods in which subjects heard only the ambient machine noise. Subjects were instructed to close their eyes and listen attentively to each performance. The subject's head was supported by a comfortable foam mold and head movement was further minimized using foam

padding and forehead restraining straps. Scanning started with the acquisition of full head, 3D SPGR (spoiled gradient) anatomical images, with the following imaging parameters: Field of view (FOV) of 26 cm, frequency-phase matrix size = 256 x 256, repetition time (TR) = 34ms, echo time (TE) = 5 ms, flip angle (FA) 45°, slice thickness 2mm, and one excitation (NEX) per phase encoding step.

For each subject, T2*-weighted gradient echo, echo planar multi-slice datasets were acquired during ON and OFF periods, with a TR of 3 sec, TE = 40 ms and FA = 90°. Twenty axial slices were acquired with matrix 64 x 64, FOV = 24 cm, slice thickness = 5 mm and inter-slice gap = 2.5 mm, yielding a voxel size of 3.75 x 3.75 x 7.5 mm. High-resolution background images (same 20 slices, matrix = 256 x 256, NEX = 2) were also acquired to overlay the functional data. The intensity level of the auditory stimulus was adjusted to a comfortable listening level for each subject prior to the onset of functional data acquisition.

4.2.5. Data Analysis

Analysis was performed on a PC running LINUX, using AFNI (Analysis of Functional NeuroImages, Medical College of Wisconsin), (Cox, 1996). Preprocessing consisted of movement correction of the functional datasets using a Fourier method, low pass filtering of the corrected time-series (cut off = 0.07 Hz) and spatial filtering of each volume using a Gaussian kernel (FWHM = 6mm). Alternating periods of baseline and listening-related activation were modeled using boxcar reference functions appropriately shifted to account for the hemodynamic response delay of

each subject. This delay was determined by examining the raw time series data. Regions of task-related activity were determined by cross correlation of the image time series with the reference waveforms. The first stage of analysis used a thresholding procedure in which voxels with correlation coefficients greater than or equal to a threshold of 0.5 were identified and retained for further analysis. The correlation values were then converted to z-scores for all task conditions and all subjects. The resulting data were transformed into the Talairach and Tournoux stereotaxic space (Talairach & Tournoux, 1988) for comparison across subjects.

The mean intensity of activation across all subjects in the *expressive* performance was compared with that in the *mechanical* performance, to look for differences in brain activation across the two tasks. The significance of these differences was determined by using a paired t-test. In order to correct for multiple comparisons, we used probability thresholding in combination with cluster size thresholding (Xiong et al., 1995). A significant cluster was defined by a set of contiguous voxels with $t > 3.16$ ($p < 0.05$), within a radial distance of 2 mm from an active voxel and that formed a minimum volume of 1050 μl (10 voxels). Images were created by mapping voxel t-values to colors using a scale from red (minimum) to yellow (maximum) when *expressive* > *mechanical* and blue (minimum) to cyan (maximum) when *mechanical* > *expressive*.

4.3. RESULTS

We analyzed the fMRI activations for the expressive versus the mechanical performances. The results are summarized in table 4.1. In the expressive listening

condition, higher intensity of activation was observed bilaterally in the transverse temporal gyri (BA 41 & 42) and the superior temporal gyri (BA 22), which included parts of primary, secondary, and associative auditory cortices (Fig 4.2). Higher intensity of activation was also observed in the right angular gyrus (BA 39), right supramarginal gyrus and right inferior parietal lobule (BA 40) as well as in the right inferior frontal cortex (including frontal operculum) (BA 44, BA 47) (Fig 4.2, 4.3). Finally, greater activation was seen in limbic association areas, including the right anterior cingulate cortex (ACC, BA 24 & 32) and in the temporal pole (BA 38) during the expressive performance. During the mechanical performance, increased intensity of activation was observed in the dorsal prefrontal area (BA 9), cerebellum (Fig 4.3) and supplementary motor area (BA 6). Stronger activation was also observed in the right parahippocampal gyrus (PHG; Fig 4.3) when subjects listened to the mechanical performance.

Area	Region	BA	Hemisphere	x	y	z	
I. Expressive Performance							
Temporal	Heschl's gyrus & STG	41	Right	55	-18	8	
		41	Left	-51	-21	8	
		42	Right	66	-10	8	
		42	Left	-67	-21	8	
	Superior Temporal Gyrus	22	Right	56	-14	2	
		22	Left	-56	-14	2	
	Parietal	Inferior parietal lobule	39	Right	49	-47	39
			40	Right	46	-47	39
Frontal	Inferior frontal gyrus	44	Right	57	10	10	
	Inferior frontal gyrus	47	Right	33	29	-16	
Limbic Association Cortex	Anterior Cingulate Cortex	24	Right	5	-2	45	
		32	Right	6	7	43	
	Temporal Pole	38	Left	-35	10	-30	
	Orbitofrontal	11	Right	5	43	-17	
		11	Left	-3	45	-17	
II. Mechanical Performance							
Limbic Association Cortex	Parahippocampal gyrus		Right	28	-16	-12	
Prefrontal Association Cortex	Superior Frontal Gyrus	9	Right	9	52	34	
		9	Left	-9	52	34	
Sensorimotor	SMA	6	Left	-3	14	62	
Other	Cerebellum		Right	33	-60	-32	

Table 4.1. Results of experiment 1. The location of activations, Brodmann's areas and Talairach x, y and z coordinates are shown.

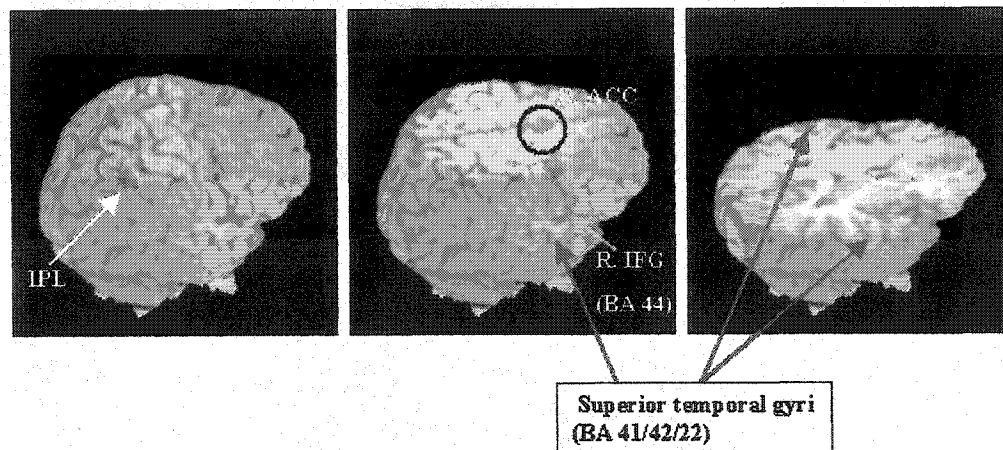


Fig 4.2. Brain areas that are more active (corrected $p < 0.05$) when musician subjects (experiment 1) listened to the expressive compared to the mechanical version of the stimuli (not all areas shown). ACC – Anterior Cingulate Cortex; IFG – Inferior Frontal Gyrus; IPL – Inferior Parietal lobule; BA – Brodmann's Area; R – Right side.

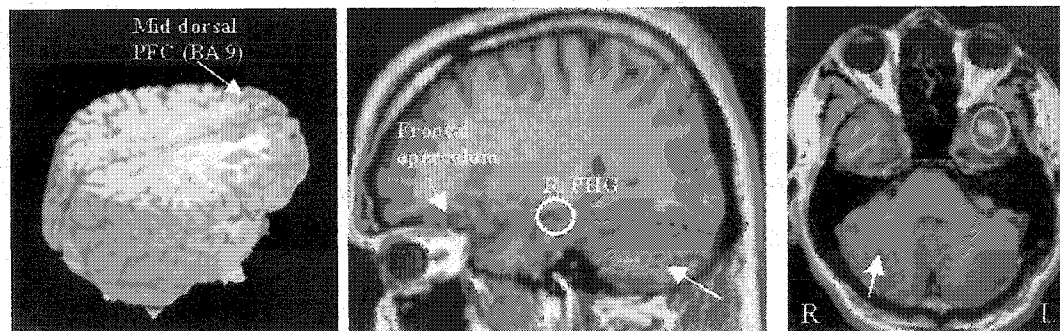


Fig 4.3. Voxels in red and yellow show brain areas that were more active (corrected $p < 0.05$) when subjects listened to the expressive performance (Experiment 1) and those in blue are areas more active when they listened to the mechanical version. PHG - parahippocampal gyrus. PFC – Prefrontal cortex; BA – Brodmann's area; Yellow arrows indicate cerebellar activity while the green circle in the right panel indicates superior temporal gyrus, BA 38.

4.4. DISCUSSION

We observed increased activity in limbic association cortex (BA 24,32,38,11) when subjects listened to the expressive performance. Limbic association cortex, particularly ACC, has been implicated in a variety of functions including emotion,

attention, and error detection (Carter et al., 1998; Bush et al., 2000; MacDonald et al., 2000). Blood & Zatorre (2001) reported that ACC activation correlated with the reported intensity of “chills” in musicians who listened to self-selected music excerpts. Thus, increased activation in these cortical areas may reflect affective or aesthetic responses of listeners to the expressive performance as observed by Repp (1999b). Increased activity in STG (BA 22) and in parietal association areas (BA 39/40) is consistent with the involvement of language mechanisms (c.f. Patel, 2003). Here we find these areas preferentially recruited in response to expressive musical performance, supporting a possible relation between musical and linguistic prosody (Patel et al., 1998). The finding of increased activity in right IFC further implies the activation of semantic language areas (Levitin & Menon, 2003), suggesting that expressive musical performance may enhance semantic interpretation of the musical material.

Greater activity of the transverse temporal gyri, including primary and secondary auditory cortices, was also observed during listening to the expressive performance. Earlier studies have provided evidence for the role of these areas in processing pitch, contour, rhythm and meter (Liegeois-Chauvel et al., 1998; Peretz, et al., 1998; Zatorre, Evans, & Meyer, 1994). However, this observation was unexpected because these areas were predicted to be equally active during both listening conditions. Increased activity was observed in the cerebellum, SMA, and prefrontal association cortex during the mechanical performance. These areas are known to be involved in the planning and execution of motor responses. It is possible, that while listening to the mechanical performance, which is inherently much less dynamic than the

expressive one, subjects focused more on the rhythm and preferentially recruited these areas.

In our second experiment, we investigated these issues in further detail. First, we attempted to replicate our findings regarding the activation of language regions and limbic association cortex with a different stimulus presentation method. Second, we addressed the issue of whether the responses of musically trained subjects generalize to musically untrained listeners. Finally, by improving our stimulus presentation and sampling methods, we hoped to reduce the interference of the magnet noise while listening to music and also determine whether the auditory cortical activity observed in the first experiment was in fact due to intensity changes between the two stimuli.

4.5. EXPERIMENT 2

A significant question that was not addressed in the first study involves the use of musically untrained subjects. It has been observed that musical training influences music listening (Schmithorst & Holland, 2003), music imagery (Lotze et al., 2003) and even the volume of neural tissue in particular cortical areas (Gaser & Schlaug, 2003). Hence it will be interesting to see whether individuals with little or no musical training (non-musicians) respond to emotionally expressive music in the same way as highly trained, professional musicians. In this experiment, we addressed the question of whether the affective neural responses of musically trained and untrained subjects are similar to one another. Seven professional musicians (mean performance experience of 27.7 years and formal training for 15.7 years.) and seven non-musicians participated in the study.

Additional issues to be addressed in the experiment concerned stimulus presentation. In the previous study, we used a block design with continuous sampling. Although extensive measures were taken to reduce noise exposure (c.f. Levitin & Menon, 2003), scanner noise was still audible during music listening, and this raised concerns regarding the quality of the listening experience of our subjects. Thus for the second experiment, we developed a method of stimulus presentation that allowed us to present entire musical performances to listeners with minimal interruption from the magnet noise. We used a variant of the sparse temporal sampling scanning technique (Hall et al., 1999) with a clustered volume acquisition time of 2 sec and an interval of 10 s between volume acquisitions. By doing so, we minimized the interference due to the scanner noise and ensured that each sample measured the response to a musical

segment that was heard in the absence of the magnet noise. In addition, given that the hemodynamic delay is usually in the order of 6sec, any effect due to the magnet noise would have died off during the following scan. According to reports from subjects, this provided a better listening environment, because the magnet noise interrupted the musical stimulus less frequently.

The study of expressive performance dictates the use of stimuli whose intensity changes. On the other hand, local changes in intensity can be extreme (Fig 4.1), raising the concern that increased activity in auditory areas, especially in primary and secondary auditory cortices, was due to intensity changes *per se* (c.f. Zatorre et al., 2002), and not due to the expressivity of stimulus fluctuations. Thus, we used an improved method for controlling the loudness level of the mechanical performance.

The root mean square (RMS) amplitude of the digitally recorded performance was calculated and applied to the mechanical version so that mean intensity of expressive and mechanical versions was identical, as was mean tempo. This enabled us to rule out the possibility that any BOLD signal change in auditory areas (e.g. BA 41 & 42) was due to difference in the overall intensity of the stimulus.

The same musical performances were used, as in Experiment 1. Stimuli were played through a Macintosh G4 laptop (Mac OS 9.0.4) using the program MAX, which synchronized stimulus delivery to acquisition of slices by triggering the scanner externally using a TTL pulse. Both the expressive and mechanical versions lasted three and a half minutes.

4.5.1. Procedure

Acquisition protocol remained the same as in Experiment 1 with the exception of the timing of collection of EPI volumes in the functional session. A sparse sampling protocol was used in which a 12 sec repetition time (TR) was combined with a 2-sec volume acquisition time (fig 4.4). This resulted in a 10 sec silent period between scans and hence provided a much better listening environment. During a single session, subjects listened alternatively to the expressive and mechanical versions, each lasting three and a half minutes during the ON phase of the block design, separated by approximately a minute of silence (OFF phase). Each version was presented twice within an 18 minute-long session and two such sessions were recorded for each subject. During the second session, the timing of the OFF blocks was shifted slightly compared to the first, so that clustered volume acquisitions sampled a different time in the musical score. By doing so, we hoped to get a better representation of the blood flow responses to the entire piece of music. Subjects were instructed to close their eyes and carefully listen to and enjoy the musical stimuli.

4.5.2. Data Analysis

Motion correction was performed separately for each session before the concatenated sessions were low pass filtered at 0.01 Hz and spatially filtered by convolving with a Gaussian kernel (FWHM = 6mm). Each stimulus type was modeled as a separate regressor in a multiple linear regression performed in each voxel. Additional nonsense regressors were included to account for signal variability due to differences in mean signal intensity and drift. The beta maps generated by regression described.

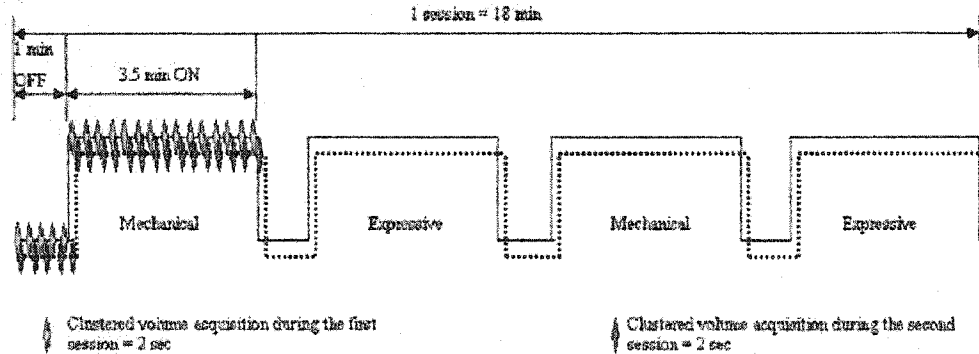


Fig 4.4 - The stimulus protocol of experiment 2. A session lasted 18 min and subjects alternatively listened to the expressive and mechanical versions, each lasting three and a half minutes during the ON phase of the block design. The ON phases were separated by approximately a minute of silence (OFF phase). During the second session depicted here by the dotted line, volume acquisition occurred at different time points (striped diamonds) compared to the first (solid diamonds), in order to get a much better representation of the hemodynamic responses to the entire stimulus. For clarity of the figure, only volume acquisition during the first ON/OFF block in both sessions is shown.

the amount of variance accounted for by each variable. After conversion to the stereotaxic space of Talairach & Tournoux (1988), the functional images were subject to two analyses. We first analyzed the data as for Experiment 1 (see Data Analysis, above) to facilitate comparison, and to validate our changes in stimulus presentation and methodology. Similar procedures were adopted to correct for multiple comparisons, and a significant cluster was defined by a set of 25 contiguous voxels ($p < 0.05$). To investigate the effects of training, we further subjected the data to a two-way analysis of variance (ANOVA) with training (musicians Vs. non-musicians) and performance type (expressive Vs. mechanical) as factors. In order to correct for multiple comparisons, we used probability thresholding in combination with cluster size thresholding (Xiong et al., 1995). A significant cluster was defined by a set of

contiguous voxels with $F > 7.81$ ($p < 0.01$), within a radial distance of 2 mm from an active voxel and that formed a minimum volume of 1365 μl (13 voxels).

4.6. RESULTS

We first compared these data with the results of Experiment 1. For both musicians and non-musicians, the mean intensity of activation across all subjects while listening to the expressive performance versus the mechanical performance was compared (Table 4.2). For both groups, this comparison revealed no differential activation in primary or secondary auditory cortices (BA 41 / 42). This indicated that our method of matching the stimuli for RMS amplitude served to adequately control the loudness of the two performances (Zatorre et al., 2002), despite local intensity differences found in the expressive version. Moreover, no increase in activation during the mechanical versus the expressive performance was observed for either musicians or non-musicians. These observations suggested that the methodological changes improved our ability to resolve responses to expressive and mechanical performances.

Area	Region	BA	Hemisphere	x	y	z
<u>Musicians -- Expressive Performance</u>						
Temporal	Superior Temporal Gyrus	22	Right	49	11	-4
Frontal	Middle frontal gyrus	46	Right	43	36	18
	Inferior frontal gyrus	47	Right	45	18	-1
Limbic Association Cortex	Parahippocampal Gyrus	35	Right	32	-14	-15
	Temporal Pole	38	Right	35	16	-24
Prefrontal Association Cortex	Superior frontal gyrus	9	Right	38	35	30
	Middle frontal gyrus	10	Right	33	58	3
Other	Red Nucleus		Right	5	-19	0
	Thalamus		Thalamus	-10	-14	0
	Cerebellum		Right	21	-26	-22
<u>Musicians -- Mechanical Performance</u>						
	None					
<u>Non-musicians -- Expressive Performance</u>						
Parietal	Posterior parietal lobule	7	Left	-33	-48	58
Limbic Association Cortex	Anterior Cingulate Cortex	24	Right	3	1	39
		24	Left	-3	-13	41
	Posterior Cingulate Cortex	29	Right	5	-54	12
		29	Left	-4	-53	12
Sensorimotor	Postcentral gyrus	2	Left	-46	-28	56
	Precentral Gyrus	4	Right	32	-21	58
	Precentral gyrus (SMA)	6	Right	3	-21	58
Occipital	Medial / Lateral occipital Gyri	18	Right	10	-69	2
		19	Right	25	-60	-10
		19	Left	-31	-81	28
Other	Cerebellum		Right	14	-66	-8
			Left	-20	-58	-10
<u>Non-Musicians -- Mechanical Performance</u>						
	None					

Table 4.2. Comparison of brain activation in subjects while listening to the expressive and mechanical versions of the stimulus in experiment 2. Brodmann's areas and the corresponding x, y and z Talairach coordinates are also shown.

When musicians listened to the expressive performance, we observed increased activity in right superior temporal gyrus (STG, BA 22), right inferior frontal gyrus (BA 47) and temporal pole (BA 38), in agreement with Experiment 1 (fig.4.5). We also observed increased activity in parahippocampal gyrus, an area where we had previously observed increased activity for the mechanical performance, conflicting with Experiment 1. In addition, we observed increased intensity in right middle and superior frontal gyri (BA 46, 9, 10), as well as in the rostral midbrain (red nucleus) and thalamus. A comparison of expressive versus mechanical conditions for non-musicians (fig.4.6) yielded a significant cluster of activation in anterior cingulate cortex (BA 24), similar to the response of musicians in Experiment 1, and also a significant response in bilateral posterior cingulate gyri (BA 24 and 29,30). Additional clusters of increased activity were found in postcentral gyrus (BA 2 - somatosensory), right precentral gyrus (BA 4 & 6 – primary motor and SMA), left superior parietal lobe (BA 7 – spatial body sense), and bilateral cerebellum. Superior occipital gyrus (BA 18,19) was also more active when non-musicians listened to the expressive performance.

A two-way ANOVA (*training X performance type*) revealed a main effect of training in several brain areas (Table 4.3; Figs 4.7 & 4.8). For musicians, greater intensity of activation was observed in the right superior temporal gyrus (BA 22), right inferior frontal gyrus (BA 44, 45), right dorsolateral prefrontal cortex (BA 46), and bilateral inferior frontal gyrus / frontal operculum (BA 47). Increased activation was also observed in the left orbitofrontal gyrus (BA 11), and bilateral superior and middle frontal gyri (BA 10).

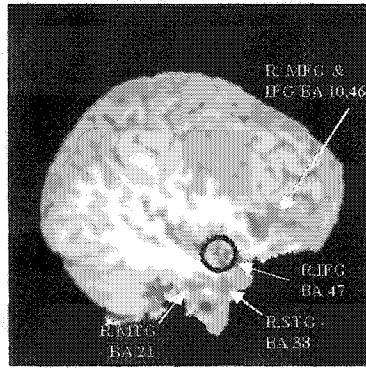


Fig 4.5. Colored voxels indicate regions of the cortex which were more active when musicians listened to the expressive performance, compared to the mechanical version, as revealed by a paired t-test at $p < 0.05$ (corrected). R – right; M – middle; S – superior; I – inferior; F - frontal; T – temporal; G - gyrus; BA – Brodmann's area.

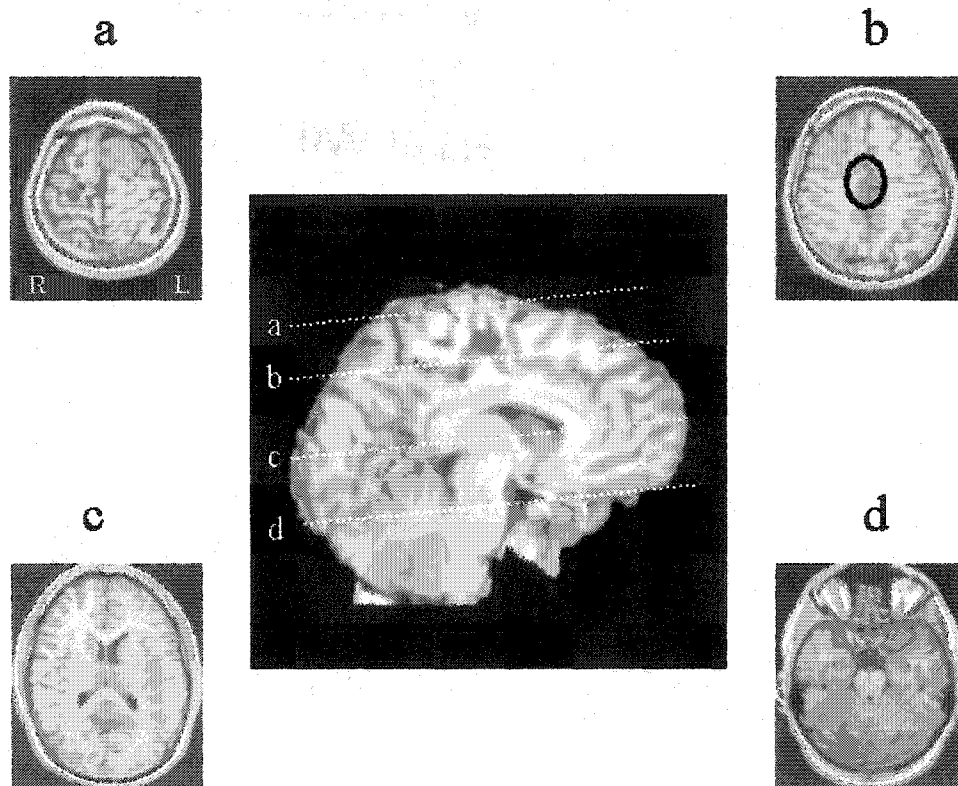


Fig.4.6. Brain regions that were more active when non-musicians listened to the expressive performance, compared to the mechanical version, as revealed by a paired t-test ($p < 0.05$, corrected). Side panels a-d are axial slices (which roughly correspond to the dotted lines in the middle panel showing a sagittal slice) showing these activations. R- right; L-left. BA – Brodmann's area. A. SMA, sensorimotor and parietal; b – anterior Cingulate; c – posterior cingulate (BA 29,30); d – Cerebellum.

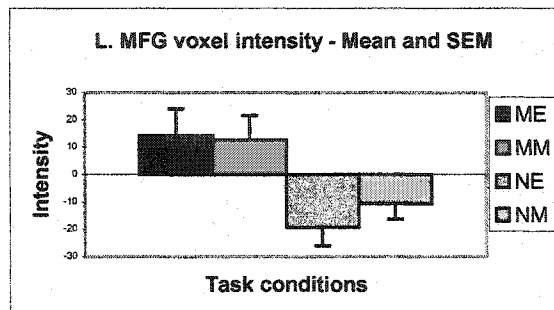
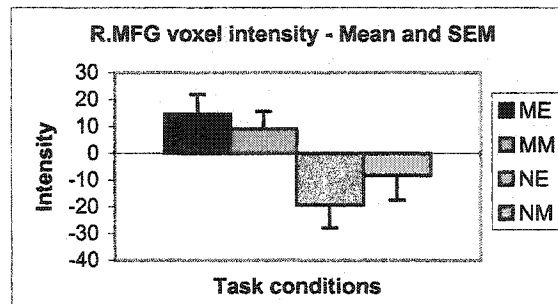
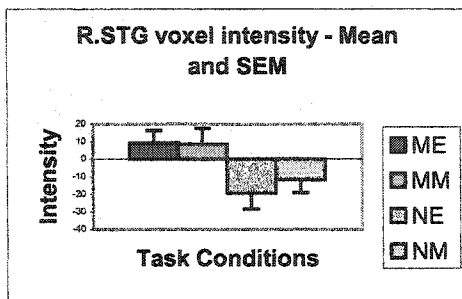
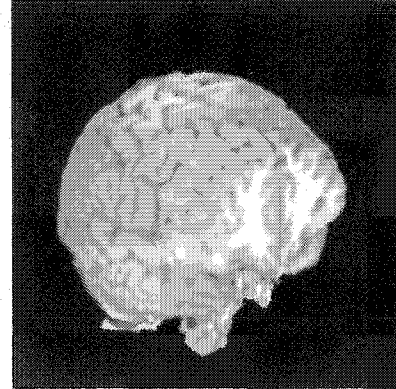
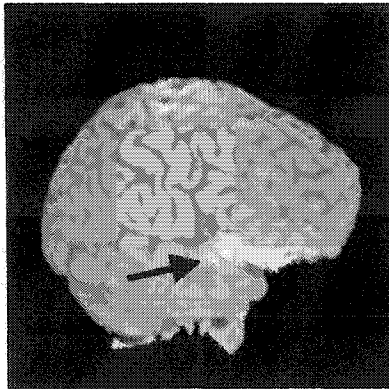


Fig 4.7. The main effect of training in the right superior temporal gyrus (BA 22, arrow in left panel), right inferior frontal (BA 44, 45,46) and bilateral middle and inferior frontal gyri (BA 10, 47) at $p < 0.01$ (corrected). The graphs show the mean intensity and standard error of mean (SEM) of the voxel with maximum intensity in these brain regions, across all subjects. ME – Musician Expressive; MM – Musician Mechanical; NE- Non-musician Expressive; NM – Non-musician Mechanical. More intense activation is observed in musicians.

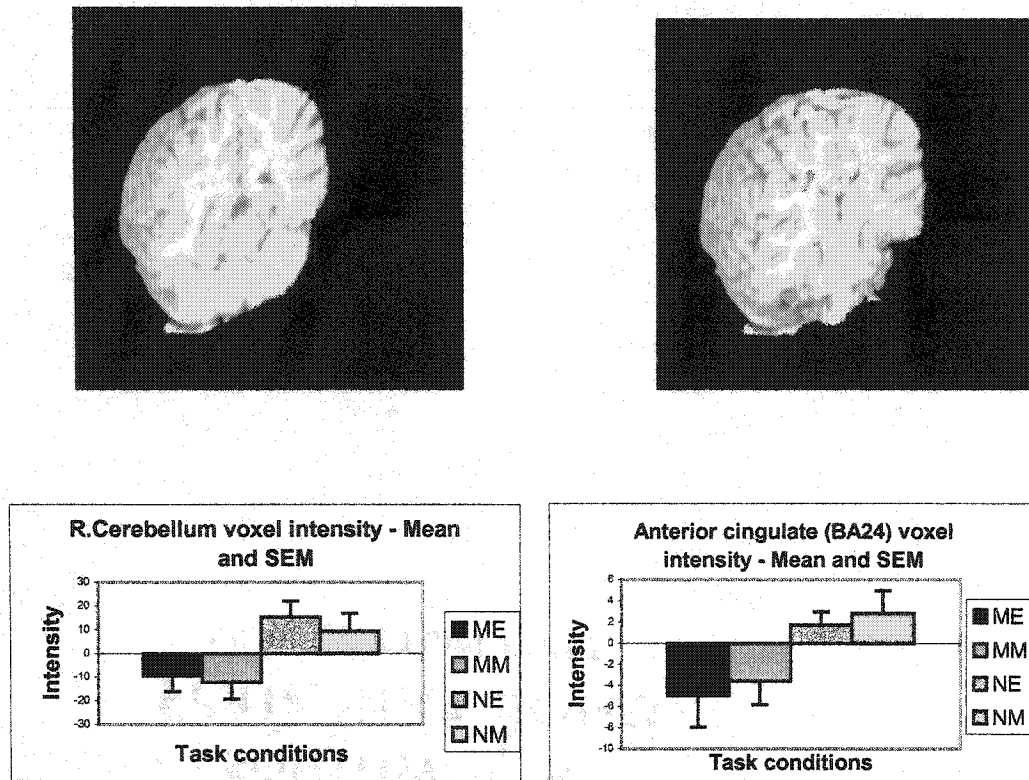


Fig 4.8. Main effect of training in the bilateral cerebellum and right anterior cingulate at $p < 0.01$ (corrected). The bar charts show the mean intensity and standard error of mean (SEM) of the voxel with maximum intensity in that brain region, across all subjects. ME – Musician Expressive; MM – Musician Mechanical; NE- Non-musician Expressive; NM – Non-musician Mechanical. More intense activation is observed in non-musicians

For non-musicians, greater activity was observed in bilateral cerebellum and right anterior cingulate gyrus (BA 24). Interestingly, no significant difference between the two groups was identified in the areas (ACC, PCC, PHG, temporal pole) that responded to the expressive performance in musicians and non-musicians. Although some significant effects of performance type turned up in the ANOVA, none of these effects survived the cluster analysis and so are not discussed further here.

Area	Region	BA	Hemisphere	x	y	z
I. <u>Musicians -- Both Performances</u>						
Temporal	Superior Temporal Gyrus	22	Right	58	7	2
Frontal	Inferior frontal gyrus	44	Right	56	13	12
		45	Right	54	16	5
		47	Right	49	23	1
		47	Left	-28	37	-6
		46	Right	50	38	0
Limbic Association Cortex	Orbitofrontal	11	Left	-25	45	-9
Prefrontal Association Cortex	Middle frontal gyrus	9	Right	46	22	33
		10	Right	20	62	-3
		10	Left	-15	49	1
II. <u>Non-Musicians -- Both Performance</u>						
Limbic Association Cortex	Anterior Cingulate Cortex	24	Right	19	-17	38
Other	Cerebellum		Right	35	-36	-30
			Left	-21	-39	-34

Table 4.3. Results of the two-way ANOVA in experiment 2. Brain regions more active in musicians and non-musicians while listening to music are shown. BA – Brodmann's areas and x, y and z Talairach coordinates are shown.

4.7. DISCUSSION

The greatest commonalities between musicians and non-musicians were observed in limbic association areas, and activity in these areas were found in both groups when listening to the musically expressive performance. Differences between musicians and non-musicians were observed in other brain areas. Bilateral frontal lobes including regions of the DLPFC, superior, middle, inferior and medial parts of the frontal lobe, were more active for musicians listening to music, and showed increased activity for the expressive performance. Interestingly, the cerebellum, sensorimotor

cortex and visual areas were predominantly more active in non-musicians when they listened to the expressive performance.

Limbic association areas were activated both in musicians and non-musicians. Non-musicians (and musicians in experiment 1) showed activity in right ACC for the expressive performance (BA 24/32), in agreement with Blood & Zatorre's (2001) observation that ACC activity correlates with the experience of intensely pleasurable experiences (chills) reported by musicians in response to self-selected musical excerpts. This observation extends this finding to non-musicians, and associates ACC activity with manipulation of a specific set of musical parameters. By way of contrast, musicians showed activation of temporal pole (BA 38) in both experiments, whereas non-musicians showed activity in PCC, an area that has been strongly linked to a variety of emotional responses (Yukie, 1995; Maddock, 1999; Maddock et al., 2003). No increase in activity was observed in limbic areas for the mechanical performance, further supporting the conclusion that limbic association cortex responded preferentially to the expressive performance. The single exception to this observation was a small area of parahippocampal gyrus (PHG) in Experiment 1. This observation was somewhat anomalous, however, because a larger area of increased PHG activity was found in musicians for the expressive performance in Experiment 2. Two previous studies reported differences in activation in PHG (Blood et al., 1999; Blood & Zatorre, 2001) and the authors concluded that activation in PHG may be specifically related to negative emotions.

Significant differences between musicians and non-musicians appeared in several different brain areas. One interesting observation in musicians was the co-activation

of areas such as the right inferior frontal gyri (BA 44, 45), ventromedial prefrontal cortex, right superior temporal gyrus (BA 22), and bilateral inferior frontal gyrus (BA 47) while listening to music. Some of these areas (right BA 22, 39/40, and 47) were preferentially activated during the expressive performance. These brain regions are known to be involved in several aspects of speech and language processing; moreover, both music and language can be considered as forms of auditory communication (Patel et al., 1998). Lesion studies also support the role of these areas, in speech and language processing. Ventromedial PFC lesions have been associated with deficits in processing vocal emotional expression (Hornak et al., 1996). Activation of the above-mentioned areas while listening to the musical composition in our study is consistent with sharing of neural resources that are important in general linguistic function, including the processing of prosodic, syntactic, and semantic coherence (Patel et al., 1998; Levitin & Menon, 2003; Tillman et al., 2003). It may also suggest that the emotional code used to convey affect in music is similar to the prosodic code used in language (Sloboda & Juslin, 2001).

Increased intensity of activation in the orbital and ventromedial PFC (BA 11) in musicians is of interest in this study for several reasons. First, these areas form part of the limbic association cortex. Second, activity in these areas has been shown in previous imaging studies to be positively correlated with intensely pleasurable experiences (chills) while listening to music (Blood & Zatorre, 2001) and also to increasingly consonant chords (Blood et al., 1999). In addition, patients with lesions in the subcallosal and ventromedial PFC have difficulty identifying facial and vocal emotional expression (Hornak et al., 1996). Previous studies have also implicated the

ventromedial PFC in judging the emotional valence of stimuli (Bechara et al., 1996; Damasio, 1996). Taken together, activation in the orbitofrontal regions in our study may point to an increased affective response in musicians while listening to music.

Bilateral frontal regions including middle, superior, and medial frontal lobes (BA 9, 10, 11) were more active when musicians listened to music, and frontal activations were stronger when musicians listened to the expressive version. A recent PET study (Platel et al., 2003) investigated musical semantic memory using a familiarity judgment task and reported increased activation in the medial frontal areas (BA 10,11). However, activation in this region is not specific to musical stimuli and medial frontal activation has been observed when subjects were asked to associate names with familiar faces (Tempini et al., 1998). It appears that activation in this region is more linked to categorization of semantic information (refer the meta analysis by Cabeza & Nyberg, 2000). The fact that our musically trained listeners were more familiar with classical music in general becomes important in this context. All musician subjects reported having heard this piece at least once, while the untrained listeners were less familiar with classical music in general, and none reported having heard this piece before. This familiarity and a cognitive appraisal of the stimulus (which might be expected from musicians) involve memory-related processes such as retrieval of episodes or recall of previously learned associations. Such processes are known to involve different areas of the PFC (Zysset et al., 2002; Koski & Paus, 2000; Oschner et al., 2002; Macdonald et al., 2000; Miller & Cohen, 2001). Retrieval of auditory memory related information has been shown to involve a

neural loop involving the auditory association and frontal cortices (Zatorre et al., 1994).

The main areas active in non-musicians included bilateral anterior cingulate and cerebellum. Previous studies have implicated different regions of the cingulate cortex in various functional domains – modulation of attention, regulation and perception of emotion, monitoring competition, complex motor control, motivation, error and novelty detection, working memory, and anticipation of cognitively demanding tasks (Devinsky et al., 1995; Carter et al., 1998; Bush et al., 2000). The posterior cingulate cortex, especially the retrosplenial cortex (BA 29,31) is implicated in the evaluation of emotionally salient stimuli (Yukie, 1995; Maddock, 1999; Maddock et al., 2003). The expressive performance of this Chopin Etude with its inherent dynamics (in loudness, tempo, rhythm) was cognitively rich a stimulus which offered several reasons for the cingulate cortex to be recruited. For instance, violation of rhythmic expectancy as the musical stimulus unfolds in time results in an apparent increase in attention (Large & Jones, 1999) and also in an increased emotional response to the stimulus (Meyer, 1956). Similarly, variation in intensity (loudness) of the expressive performance could also result in varying levels of attention capture.

In the expressive versus mechanical comparison, several areas such as the sensorimotor cortex, SMA and superior parietal lobe were significantly active in non-musicians in addition to the cerebellum. Blood & Zatorre, (2001) reported that activity in the cerebellum and SMA correlated with ratings of chill intensity while listening to their favorite pieces of music. Although the authors gave no functional

interpretation for this activation, recruitment of brain regions involved in timing and motor planning may suggest that non-musicians focused more on the rhythmic aspects of music. This may arise from tracking the beat or following the rhythm, which constitute an integral part of listening to music (Large & Jones, 1999, Large & Palmer, 2002).

Visual association areas (BA 18 and 19) in the superior occipital, lingual and fusiform gyri were more active when non-musicians listened to the expressive version compared to the mechanical. These areas are known to be active during pitch judgment tasks (Zatorre et al., 1998), harmonic processing (Schmithorst & Holland, 2003), visuospatial or visual imagery tasks (Kosslyn et al., 2001) and also in detection of pitch changes in a sequence of sounds (Platel et al., 1997). It is likely that listening to the expressive performance involved some or all of these activities. The importance of these visual association areas in auditory processing is also highlighted by the fact that subjects with lesions of the fusiform gyri become impaired at auditory recognition tasks (Clarke et al., 2002).

Though the results of the second experiment are different in certain ways from those of the first, we find many similarities too. It should be borne in mind that there were methodological differences between the two experiments that would have contributed to the observed differences in activation. The modified sparse sampling technique reduced interference due to the background magnet noise, and by sampling at different time points during the second session we got a better representation of the BOLD response to the entire piece of music. Differential brain activation was observed in musicians and non-musicians (Inferior frontal / orbitofrontal, temporal

pole, hippocampus / parahippocampal gyrus in musicians compared to anterior and posterior cingulate in non-musicians). This might conceivably be related to the difference in the way musicians and non-musicians perceived expressive cues in these stimuli. Our findings raise the possibility that music communicates affect in a way that is distinct from other emotional experiences. This would also offer indirect support for the theory that musical experiences tend to produce non-specific affective arousal (Shacter & Singer, 1962), which may or may not be interpreted as emotion, rather than directly communicating identifiable emotions. Sloboda & Juslin (2001) call the interplay of tension, release and confirmation in response to music as “proto-emotion”, as it has a strong tendency to grow into emotions through mental appraisal. In other words, it is semantic content or a context-relevant cognitive appraisal that turns structure-induced proto-emotions into full-blown emotions.

4.8. Conclusions

We identified both similarities and differences in the way musicians and non-musicians perceive music. Results confirm that manipulations of a set of physical parameters of the stimulus (intensity and timing; expressive cues) that musicians incorporate in a music performance to make it aesthetically more appealing, resulted in activation of the limbic and paralimbic regions. We also found that musical training and familiarity with this musical style play an important role in determining brain activations. Musicians’ brain activation apparently reflects language-like responses, perhaps familiarity with this style of music, and even appraisal of performance quality. Non-musicians seem to concentrate more on the rhythmic

aspects of music, as evidenced by activation of brain regions involved in timing and movement planning. On the whole recruitment of neural structures related to components of attention, emotion and evaluative judgment as observed in this study may help us understand better, the process of musical communication between the performer and the listener.

Chapter 5

Brain networks underlying sensorimotor coordination and timing in Parkinson's disease

5.1. INTRODUCTION

Everyday life is full of instances where we interact effectively with our surroundings based on our estimate of time. Perception and production of time is so integral a part of our life that deficits in these domains usually result in a significant reduction in a person's quality of life. Parkinson's disease is one such debilitating illness. It is believed that the degeneration of Substantia Nigra pars compacta with subsequent depletion of dopamine in the putamen and the resulting disruption of basal ganglia-thalamocortical loops produces the classic motor signs and symptoms in PD. However, the traditional view of the role of these dopaminergic pathways as a pure motor system seems too limiting, given their increasing role in timing and cognitive processes that underlie goal-directed action (Harrington et al., 1998; Harrington & Haaland 1999). Recent studies have focused not only on the basal ganglia-thalamocortical system, but also on the mesocorticolimbic dopaminergic system, originating in the Ventral Tegmental Area and Substantia Nigra - pars compacta, and other cortico-cortical connections (parietal, premotor and frontal) (Samuel et al., 1997; Sabatini et al., 2000; Mattay et al., 2002). How different cortical and subcortical regions are affected in Parkinson's disease and how these regions organize themselves to compensate for the motor and cognitive insufficiencies are not yet clearly known.

These questions become more interesting in light of previous observations that movement coordination in Parkinson's disease patients improves when cued by an external rhythmic auditory stimulus (Thaut et al., 1996; McIntosh et al., 1997; Johnson et al., 1998).

5.1.1. Neural correlates of timing

Identifying the neural correlates of timing has gained renewed interest after the advent of functional imaging techniques such as Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI). Two neural structures that are the corner stones of the internal timing system are the cerebellum and the basal ganglia (Meck, 1996; Ivry, 1997). Both structures form reciprocal loops with many cortical areas (Alexander et al., 1986; Middleton & Strick, 1997 a;b), which enable them to provide the precise representation of temporal information across a range of different task domains.

The time-keeping operations in the BG are supported by converging findings from lesion (Artieda et al., 1992; Pastor et al., 1992; Meck, 1996; O'Boyle et al., 1996; Harrington et al., 1998; Malapani et al., 1998), pharmacological (Meck, 1986; Rammsayer, 1989) and functional imaging (Jueptner et al., 1995; Rao et al., 1997; Schubotz et al., 2000; Mayville et al., 2002; Nenadic et al., 2003) studies. However, several studies on Parkinson's disease patients yield ambiguous results. While some studies reported Parkinson's disease patients' performance to be similar to age-matched controls in terms of overall variability during the continuation phase (Ivry & Keele, 1989), study of bimanual movements (Johnson et al., 1998) found that they

were significantly worse in the absence of external cues. Previous studies have reported that motor delay timing in medicated Parkinson's disease patients is normal (Harrington et al., 1998; O'Boyle et al. 1996). Evidence for cerebellar involvement in timing has been shown in several studies. Patients with cerebellar damage were shown to exhibit increased variability in the timing component of the finger-tapping task, as well as decrements in discrimination of auditory intervals (Ivry & Keele, 1989) and exhibited an increased threshold for auditory duration discrimination. Ivry et al. (1988) reported that patients with lateral cerebellar damage showed increased variability in the timing component of a motor task, while those with medial cerebellar damage showed high variability in motor implementation.

Taken together, the above results suggest a role for both cerebellum and BG in certain timing-related operations and show that lesions in these regions result in varying levels of impairment. However, no clear functional distinction exists between the two brain regions in timing-related operations and an overlap of function seems more probable. The inconsistency of results and the absence of a clear line of functional demarcation in the timing literature bring up a few questions concerning temporal processing – 1) Does timing rely on a single network that includes structures such as basal ganglia or cerebellum, or on a distributed process mediated by different neural areas depending on dynamic aspects of timing? Parkinson's disease patients form an ideal population to explore this question since their deficit lies mainly in the basal ganglia. 2) Are the networks used for time perception and production context-dependent? 3) Is it possible that networks are plastic enough to change functional

connectivity according to the lesion or deficit (for instance Parkinson's disease), in order to compensate for the loss of function?

5.1.2. Paradigms: Syncopation-Synchronization and Continuation

The present study aims at identifying brain regions involved in timing in Parkinson's disease patients as revealed by a simple (synchronization) and a relatively complex (syncopation) timing task. In principle, the performance of both synchronized and syncopated behavioral patterns requires one to generate a rhythmic response sequence at the metronome rate and then shift the onset times appropriately to produce the correct phase relationship with the stimulus. But in practice, shifting the responses by 180° to produce a syncopated pattern is difficult even at slow movement rates. In fact at higher rates of syncopation ($>2\text{Hz}$), subjects show a spontaneous switch to synchronization to stay coordinated with the metronome (Kelso et al., 1990; 1992). Even at lower rates, evidence suggests that there is a higher attentional load associated with syncopation (Carson et al., 1999; Temprado et al., 2002). Constraints on the ability to syncopate may arise because one has to predict not only when the next metronome beat will occur, but also the time point that bisects the interval between successive tones. Furthermore, although timing accuracy during synchronization is defined with respect to a single metronome beat, evaluating one's performance during syncopation requires knowledge concerning the temporal relationship between each movement and the two tones that bound the interval (Mayville et al., 2002). This delay in feedback during syncopation may impose additional demands on working memory. Thus syncopation behavior may be

organized on a cycle-to-cycle basis, independently for each metronome beat, in contrast to synchronization that may be organized as a continuous rhythmic sequence. The syncopation-synchronization task addresses two questions relevant to motor coordination in Parkinson's disease. First, do Parkinson's disease patients use different neural networks to support similar temporal information under the two different timing contexts of synchronization and syncopation? If so, are these different from that observed in normal adults? Second, do the additional memory and attentional requirements of syncopation recruit alternate pathways in Parkinson's disease patients compared to normal adult subjects?

The continuation task first employed by Stevens (1886) and popularized by Wing and Kristofferson (1973) has provided a process model for evaluating component sources of temporal variability (clock and motor) in performance. In this task, once a temporal pattern (usually isochronous) is initiated using an auditory or visual pacing phase, subjects continue tapping at the same rate in the absence of pacing. We have previously studied a group of normal adult volunteers combining the synchronization-syncopation paradigm with the continuation paradigm (Jantzen, Steinberg & Kelso, 2002b). Although the motor demands for both modes of coordination remain the same, syncopation resulted in a different pattern of neural activation compared to synchronization. These differences persisted during their respective continuation phases too showing that context plays an important role in determining brain activation (Jantzen, Steinberg & Kelso, 2002b). In the present study, we use the continuation paradigm for both coordination tasks (synchronize and syncopate) to see

whether the same network of brain areas that supports timing and movement during pacing would do so, during the respective continuation phase when the metronome is removed. This is relevant in Parkinson's disease for two reasons. First, Parkinson's disease patients perform better in coordination tasks when paced than otherwise; Second, it is not known how the cognitive decline in Parkinson's disease affects performance, since continuing coordination requires reference to representation of intervals in short-term memory. Since the patient group was comprised of elderly subjects, we also scanned a group of age-matched control subjects to differentiate the effects of the disease process from those due to aging.

5.2 METHOD

5.2.1. Subjects

Eleven (8 males, 3 females) right-handed subjects, mean age 74.09 years (SD = 10), diagnosed with mild to moderate, idiopathic Parkinson's disease and five age-matched control subjects (age = 77.6 ± 3.01 years) participated in the study. None of the subjects had a history of stroke, dementia, psychiatric illnesses, head injury, any surgical procedure for treatment of PD or severe arthritis preventing them from doing the task. Patients were assessed using the Unified Parkinson's Disease Rating, UPDR – motor examination items 20-25 (Fahn et al., 1987), modified Hoehn and Yahr (Hoehn and Yahr, 1967) and Schwab and England activities of daily living (ADL) (Schwab and England, 1969) scales to determine the severity of their disease and disability. The demographic and clinical details of our patients are given in table 5.1.

All patients were tested during the “ON” phase of medication. Control subjects were active and healthy for their age and none of them had a history of neurological or psychiatric illnesses nor was taking any medication for neurological disorders. The experimental protocol was set under NIH guidelines and was approved by the University Institutional Review Board. All subjects signed an informed consent before participating in the study.

Subject	Age	Sex	Onset (yrs)	UPDR						HY	SE	Medication
				20	21	22	23	24	25			
1	82	M	7	2	1	1	1	1	1	3	60%	Sinemet, Requip
2	74	M	8	2	1	1	1	1	1	1.5	90%	Sinemet, Mirapex, Symmetryl
3	72	M	3	1	1	1	1	1	1	2	90%	Sinemet
4	70	F	4	2	0	1	0	1	1	1	100%	Eldepryl
5	73	M	3	0	0	1	1	1	1	3	80%	Eldepryl, Mirapex
6	86	M	5.4	0	0	0	1	1	1	1	90%	Sinemet
7	79	M	6	0	0	1	1	1	1	2.5	80%	Sinemet
8	47	M	4	2	1	0	1	1	1	1	90%	Sinemet
9	73	F	2.5	1	1	1	1	1	0	1	100%	Mirapex
10	83	F	3	0	0	0	0	0	0	2	90%	Mirapex, Eldepryl
11	76	M	4	2	2	2	2	2	2	2.5	80%	Sinemet, Mirapex, Eldepryl

Table 5.1. Clinical and demographic data of Parkinson's disease patients. Examination included the Unified Parkinson's Disease Rating (UPDR) scale (motor examination section – questions 20-25), Hoehn and Yahr (HY) scale and Schwab and England (SE) activities of daily living.

5.2.2. Task

All Parkinson's disease patients and control subjects were first given a detailed description of the experiment and their task. Then they had a practice session before

entering the scanner during which they listened to the metronome and performed both the synchronization and syncopation tasks. Subjects' motor behavior was monitored to make sure that they understood the task instructions. While in the scanner, subjects listened to a series of beeps (1000 Hz sine tones; 60 ms duration) and task instructions through a headphone. Behavioral responses were recorded using an air-filled pillow placed between their right index finger and thumb. A pressure transducer converted changes in air pressure in the pillow to voltage and was recorded using a computer. There were three tasks: one listening, and two coordination tasks - Synchronization and Syncopation. Both synchronization and syncopation tasks had a pacing and a continuation phase. Subjects were asked to close their eyes and listen to the beeps carefully during all the tasks. During the listening task, subjects listened to the beeps only and made no motor responses. During the pacing phase of the coordination tasks, subjects coordinated their movement responses (pressing the air pillow) to a series of tones presented at a constant rate of 1.25 Hz. The tones were then discontinued and subjects were required to continue moving at the same rate until they heard a 1-sec long tone, which signaled them to rest until the beginning of the next pacing task. Subjects were instructed to make finger movements such that during paced synchronization, the point of peak movement coincided with the tone, and during paced syncopation, such that each movement occurred exactly in between successive tones. Regardless of the coordination pattern (synchronize or syncopate) during pacing, subjects were instructed to maintain the same movement rate as accurately as possible during continuation.

5.2.3. Image acquisition protocol

Blood oxygenation level dependent (BOLD) effects were measured using echo planar imaging on a 1.5 Tesla GE Signa scanner (General Electric Medical Systems, Milwaukee, USA). Twenty, axial high-resolution SPGR images 5mm thick and spaced 2.5 mm apart, provided background anatomy for overlay of function (Echo Time = in phase; Repetition Time = 325ms; Flip Angle = 90^0 ; Field of view = 24 cm; Frequency x Phase matrix = 256x256; Number of excitations (NEX) = 2). Echo-planar images were acquired using a single-shot, gradient-echo, echo planar pulse sequence (Echo Time = 60ms; Repetition Time = 3s; Flip Angle = 90^0 ; Field of view = 24 cm; 64x64 matrix) at the same 20 axial locations as the background images. Finally, full head 3D SPGR images (2mm thick contiguous 110 axial slices; were acquired using the following parameters – Echo Time = 5ms; Repetition Time = 34ms; Flip Angle = 45^0 ; Field of view = 26 cm; 256x256 matrix). A modified block design was employed in which a single block was comprised of a rest period (8 TR = 24 sec), followed by pacing and then continuation (7 TR or 21 sec each). Each task started with a rest (OFF) period and had six ON/OFF blocks followed by an additional rest period at the end and lasted seven minutes (140 TRs). All subjects did the listening task first, in order to become familiar with the beeps. The order of synchronize and syncopate blocks was randomized such that half the subjects did synchronization first and the other half, syncopation.

5.2.4. Behavioral Analysis

The point of maximum compression on the pillow (peak flexion of the index finger and thumb) defined the time of the behavioral response. The time of each response was corrected by 30ms to account for the temporal delay of the pneumatic device as determined by the length of the tube and the speed of sound in air. Two relative measures of performance were calculated. Inter-response-interval (IRI) was defined as the time between consecutive behavioral responses and relative phase was defined as the time between each behavioral response and the preceding stimulus onset, divided by the stimulus period (Zanone & Kelso, 1992). Statistical analysis including t-tests and Analysis of Variance (ANOVA) were done using these two parameters. In addition, variance and lag-one autocovariance measures were calculated on IRI during continuation, according to the two-process model of Wing & Kristofferson (1973) in order to detect relative changes in variability of the putative central clock and motor mechanisms.

5.2.5. Neuroimaging analysis

Data analysis was performed mainly using AFNI (Analysis of Functional NeuroImages, Cox, 1996). Preprocessing included motion detection and correction followed by spatial smoothing with a Gaussian kernel (FWHM = 6mm) and temporal low pass filtering at 0.1 Hz. Multiple regression was used to determine the relative contribution of pacing and continuation model functions to the observed time series for each voxel. Model time series consisted of vectors comprised of ones when the stimulus was present (pacing or continuation) and zeros during rest, convolved with a

hemodynamic response function. The resulting fit coefficient for each regressor of interest was divided by the average offset of each voxel to give a measure of percentage signal change. SPM99 (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, London) was employed to coregister functional images to full head 3D anatomical images. Images were then transformed to the coordinate space of Talairach and Tournoux (1988) using AFNI, before further statistical evaluation.

Significant differences between experimental conditions were assessed by a two-way ANOVA with factors of task (listen, synchronize, syncopate) and mode (pace, continue). The resulting maps were thresholded at a corrected p value of < 0.001 and clustered using a volume of $525 \mu\text{L}$. This threshold was established based on 1000 Monte Carlo simulations demonstrating that the probability of obtaining such an activation cluster for an entire volume (type I error) was less than 0.0001 (Xiong et al., 1995).

5.3. RESULTS

5.3.1. Behavioral performance in patients and age-matched control subjects

All Parkinson's disease patients and control subjects reported the synchronization task to be easier than the syncopation task and found the metronome at 1.25 Hz too fast to accurately perform the syncopation task. Analysis of the relative phase between the

pacing tones and the behavioral response corroborated these reports. Behavioral responses during synchronization and syncopation in one Parkinson's disease patient are shown in fig.5.1. Synchronization responses (upper panel) are quite consistent and occur in synchrony with the beeps, while syncopation (lower panel) is highly variable. The mean and standard error of mean (SEM) of the relative phase during paced synchronization and syncopation in patients and controls are plotted in fig.5.2a and the variability of relative phase during these tasks in fig.5.2b. The mean relative phase in patients for paced synchronization was $8.98^{\circ} \pm 8.2^{\circ}$ and that for paced syncopation was $37.65^{\circ} \pm 33.9^{\circ}$. The variability of the relative phase in patients during paced synchronization ($27.7^{\circ} \pm 4.9^{\circ}$) and paced syncopation ($58.3^{\circ} \pm 6.1^{\circ}$) were significantly different ($p < 0.00095$; $t_{20} = -3.87$). For control subjects, the mean relative phase for paced synchronization was $17.93^{\circ} \pm 14.1^{\circ}$ and that for paced syncopation was $57.86^{\circ} \pm 45.3^{\circ}$. The variability of relative phase in control subjects during paced synchronization ($24.46^{\circ} \pm 4.4^{\circ}$) was significantly different from that for paced syncopation ($51.53^{\circ} \pm 8.9^{\circ}$) at $p < 0.02$ ($t_8 = -2.7$). As can be seen in fig. 5.2b, both patients and age-matched controls were highly variable in their performance of the syncopation task.

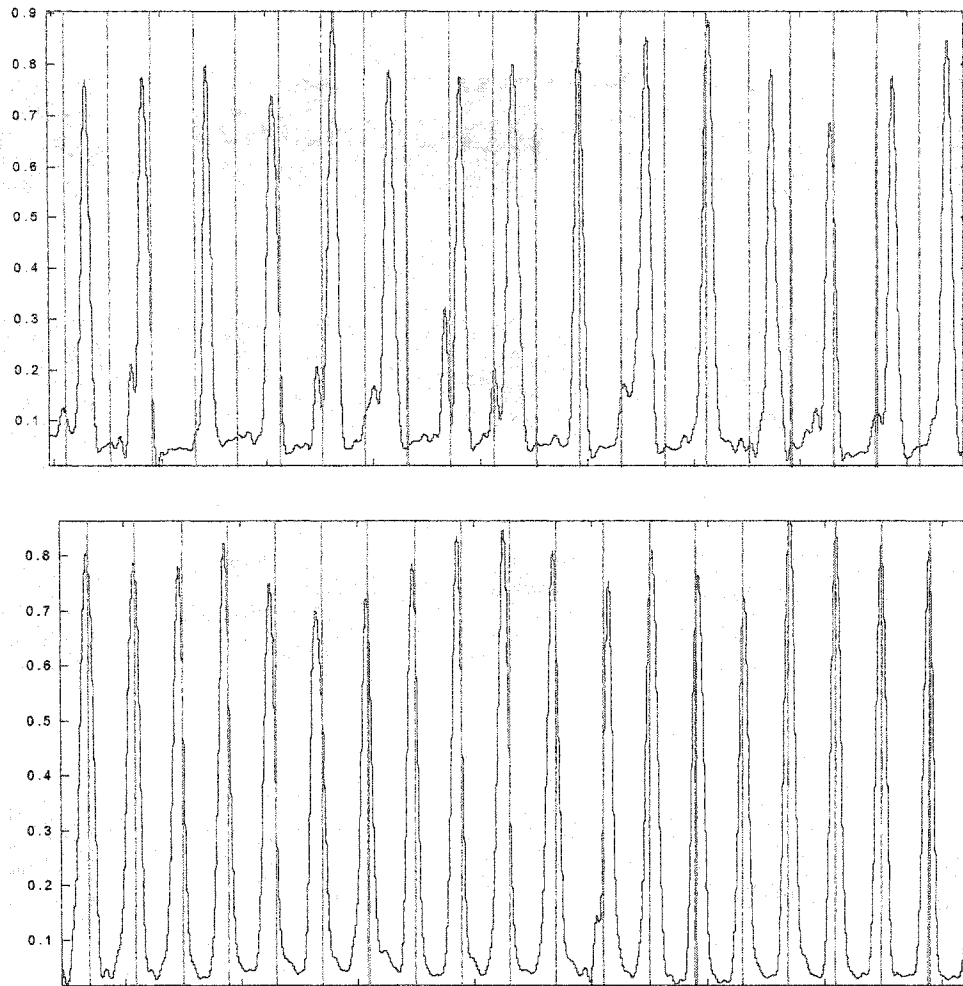


Fig. 5.1. Behavioral responses (black) from one Parkinson's disease patient during one block of paced and continued syncopation (upper panel) and synchronization (lower panel). Blue lines indicate beeps during the pacing phase and the red lines indicate the position of the beeps had they been presented during continuation. Consistent timing can be seen during synchronization both during pacing and continuation, while behavior is quite variable during syncopation. The Y – axis shows the amplitude of the responses scaled between 0 and 1.

Both patients and controls subjects were able to maintain an inter response interval (IRI) closer to the required IRI (800ms) during most of the tasks. The mean and SEM of IRI during all the tasks are plotted in fig. 5.3a (see also table 5.2). Patients had a tendency to slow down during the continuation tasks while responses of control subjects were generally faster than the metronome for the syncopation tasks.

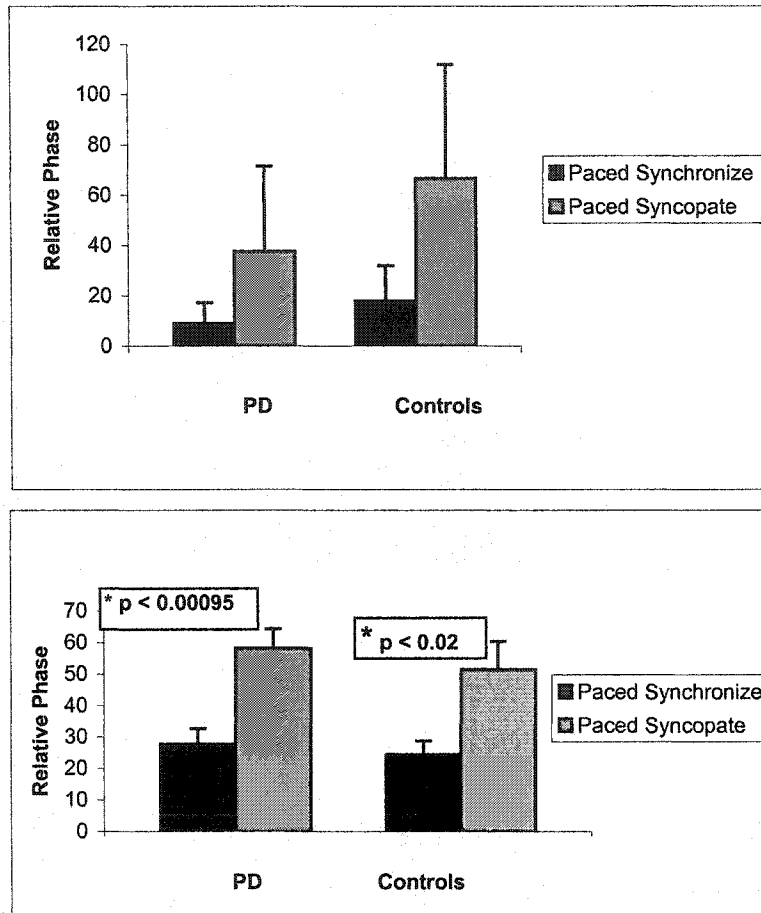


Fig. 5.2. Mean and standard error (SEM) of relative phase (upper panel) in Parkinson's disease patients and age-matched control subjects. Both patients and control subjects performed the synchronization task relatively well compared to syncopation. The relative phase during syncopation is far from the required value and shows high variability. Variability of relative phase in both groups of subjects during paced synchronization and syncopation is shown in the lower panel. As can be seen, the variability during paced syncopation was significantly different (* p value) from that during paced synchronization in both groups.

A two-way Analysis of Variance (ANOVA) of IRI in PD patients, performed using task (synchronization, syncopation) and mode (pacing, continue) as factors, revealed a main effect of mode ($p < 0.019$; $F_{1,40} = 5.94$). There was no main effect of task or interaction. This is in fact evident in fig.5.3a, which shows that patients consistently slowed down during continuation of both synchronization and syncopation, compared

to the respective pacing tasks. Fig. 5.3b shows the variability of IRI in Parkinson's disease patients during all the tasks.

Task	Parameter	PD patients	Control subjects
Paced synchronization	IRI	794.1 \pm 2.47	798.3 \pm 2.05
	Variability	54.6 \pm 16.7	40.1 \pm 14.4
Continued synchronization	IRI	829.4 \pm 15.2	808.6 \pm 27.2
	Variability	50.5 \pm 15.2	49.4 \pm 8.1
Paced syncopation	IRI	807.7 \pm 13.6	748.5 \pm 62.5
	Variability	96.9 \pm 29.2	74.8 \pm 14.5
Continued syncopation	IRI	851.7 \pm 27.7	775.5 \pm 80.2
	Variability	64.2 \pm 19.3	62.5 \pm 12.5

Table 5.2. Inter Response Interval (IRI) and its variability (Mean \pm SEM) during all tasks in PD patients and control subjects.

A two-way ANOVA on the variability of IRI in patients (table 5.2) revealed a main effect of task ($p < 0.0009$; $F_{1,40} = 12.94$), and mode ($p < 0.02$; $F_{1,40} = 5.56$) but no interaction. As can be seen in fig.5.3b greater variability in behavior occurred during syncopation than synchronization, which corroborates the report of patients that syncopation was more difficult than synchronization. Nevertheless, patients exhibited more variability in IRI during paced syncopation than while continuing syncopation.

A two-way ANOVA on mean IRI in control subjects did not reveal a significant main effect or interaction. However, an ANOVA on the variability of IRI (table 5.2) in control subjects revealed a main effect of task ($p < 0.0007$; $F_{1,16} = 17.8$), indicating a larger variability during the syncopation task compared to synchronization, irrespective of whether the movements were paced or continued. In order to compare the behavioral performance of PD patients and control subjects across all tasks, we

also performed a 3-way repeated measures ANOVA on IRI with group (patients or control), task (synchronize or syncopate), and mode (pace or continuation) as the three factors. The only significant result was a main effect of mode ($F_{1,14} = 4.62$, $p < 0.05$). Post hoc analysis using Tukey's studentized range test revealed that the mean IRI during the continuation tasks was significantly ($p < 0.05$) larger than that during pacing.

Analysis of the data variance and auto-covariance according to the Wing-Kristofferson model yielded the following results. A paired t-test to compare the mean clock and motor variance (fig.5.3c) during continuation of synchronization and syncopation revealed no significant differences in either variance between the two conditions. This two-process model predicts that the lag-one autocorrelation ($\text{Acorr}(I(1))$ = correlation between adjacent pairs of intervals in a sequence of intervals) should be $-1/2 < \text{Acorr}(I(1)) < 0$. Our data showed that only data from 45.5 % of Parkinson's disease patients were within these limits. This could be due to failure of the model's independence assumptions (between clock and motor variability) in these data (for a discussion see Wing, 2002). Our data from PD patients indicate that the use of alternative coordination patterns during pacing does not affect variability in the underlying timing process or in the independent motor delay, according to the two-process model proposed by Wing and Kristofferson.

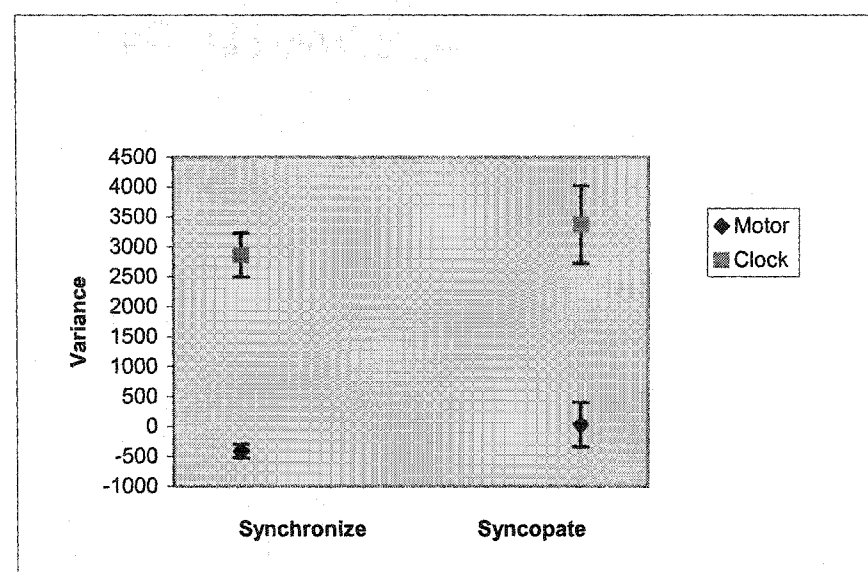
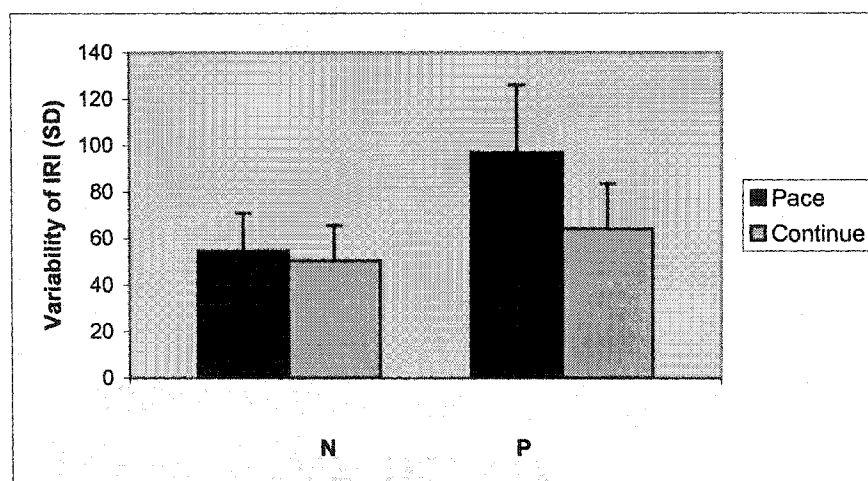
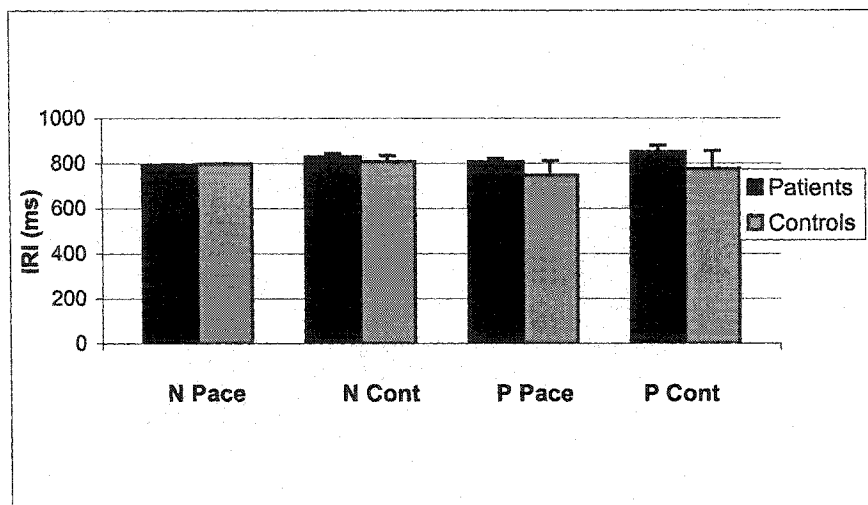


Fig. 5.3. Mean inter response interval (IRI) during all tasks (upper panel) in patients and age-matched control subjects. Both groups of subjects were able to maintain the required IRI of 800ms, although the performance during the syncopation task was more variable. Patients responded slowly (larger IRI) during the continuation phase of both tasks, while control subjects were faster during syncopation. Variability of IRI during all tasks in Parkinson's disease patients is shown in the middle panel. The two tasks (synchronize and syncopate) and modes (pacing and continuation) were significantly different. The paced modes of coordination (both synchronization and syncopation) showed more variability than the continuation phases. The lower panel illustrates the results of data analysis using the two-process model of Wing and Kristofferson. The mean clock and motor variance in PD patients were not significantly different during the two coordination modes. However, note the larger clock and motor variance (and more error) during the syncopate condition compared to synchronization. N – Synchronize; P – Syncopate; Cont – Continue.

Summarizing the analysis of behavioral data, it can be stated that (i) Parkinson's disease patients were able to maintain the required tapping interval (IRI) much better when paced than otherwise (no similar effect was found in control subjects) (ii) Both patients and age-matched controls were more variable (variability of IRI) during syncopation compared to synchronization and patients alone were more variable during pacing compared to continuation (iii) Patients and controls were more consistent while moving on the beep than exactly in between the beeps (as shown by variability of relative phase). The behavioral response also revealed that in general, subjects found it easier to maintain the required interval when they had pacing information available than in their absence.

5.3.2. Neuroimaging

5.3.2.1. Parkinson's disease patients

A 2-way ANOVA revealed a main effect of task and a main effect of mode. There was no significant interaction between these effects. The main effect of task was observed in a large number of cortical and subcortical areas. Post-hoc t-tests were

performed in order to characterize the contributions of the three different levels of task (Listen - L, synchronize - N, syncopate - P) to the main effects seen in the ANOVA. Fig.5.4 depicts the differences between different levels of task at a corrected $p < 0.001$. Subtracting activation during the listen condition from that during syncopate and synchronize helps identify BOLD changes in brain areas due to the motor tasks alone, excluding changes related to perception of the auditory metronome. It can readily be seen that the syncopate task recruited the maximum number of brain areas (column 2 of fig.5.4). Cortical areas activated during syncopation include a large cluster of activation in bilateral primary sensorimotor cortices extending posteriorly and inferiorly into inferior and superior parietal lobes (IPL – BA 40; SPL, Brodmann's area BA 7) with larger activation in the left hemisphere, supplementary motor area (SMA), bilateral superior frontal gyrus (SFG - BA 9,10) extending inferiorly into the middle and inferior frontal gyri in the right hemisphere, paracentral lobule and cingulate gyrus (BA 24), angular gyrus (BA 39), supramarginal gyrus (BA 40), posterior cingulate (BA 29), bilateral primary and secondary auditory areas (Superior Temporal Gyrus , Transverse Temporal Gyrus, BA 41,42,22), middle temporal gyrus (MTG; BA 21,37) and bilateral lingual gyri (BA 18/19). Significant activation was also observed in the left thalamus (pulvinar, ventral lateral and medial dorsal nuclei – VLN and MDN) and right putamen. Widespread activity in the cerebellum was observed in culmen, declive, tonsil, inferior semilunar lobule and the dentate nucleus. Column 3 of fig.5.4 shows brain areas that were more active in syncopation than synchronization. These include the

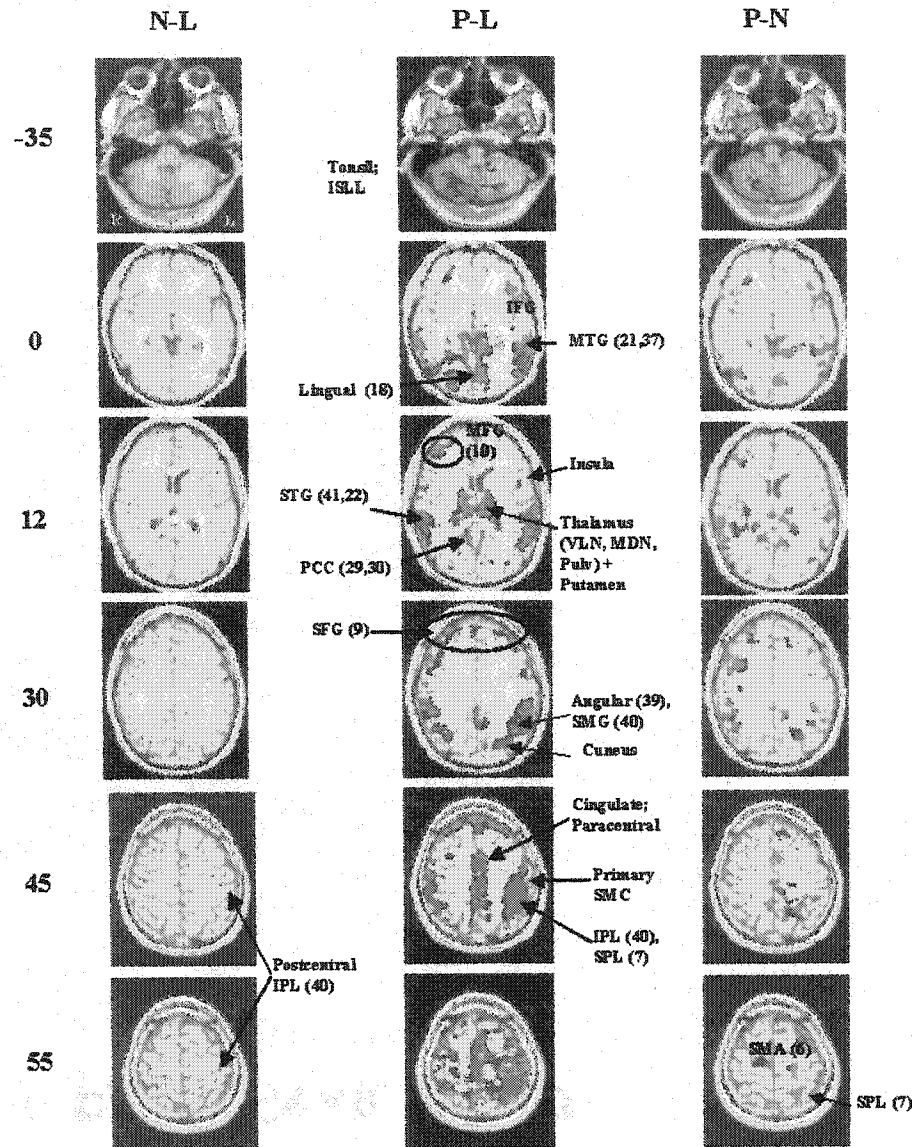


Fig. 5.4. Contribution of different task conditions to the main effect of task (Listen, Synchronize, Syncopate) in Parkinson's disease patients. Activation in selected axial slices shown at a corrected $p < 0.001$. The vertical Talairach coordinate is shown beside each axial slice. The first column shows the brain areas more active during synchronization compared to the listen task (N-L). The second column shows areas more active during syncopation compared to listening (P-L) and the third column shows areas more active during syncopation compared to synchronization (P-N). The numbers within brackets indicate the corresponding Brodmann's areas. ISLL – Inferior SemiLunar lobule of the Cerebellum; MTG – Middle Temporal Gyrus; STG – Superior Temporal Gyrus; IFG – Inferior Frontal Gyrus; MFG – Middle Frontal Gyrus; PCC – Posterior Cingulate Cortex; VLN – Ventral Lateral Nucleus; MDN – Medial Dorsal Nucleus of thalamus; Pulv – Pulvinar; SFG – Superior Frontal Gyrus; SMG – Supramarginal gyrus; SMC – Sensorimotor Cortex; IPL – Inferior Parietal Lobe; SPL – Superior Parietal Lobe; SMA – Supplementary Motor Area.

cerebellum, thalamus, putamen, superior temporal gyrus, posterior and anterior cingulate, inferior and superior parietal lobe, SMA and premotor cortex. It may be noted that the observable differences in activation between columns 2 and 3 of fig.5.4 indirectly represent brain areas active during the synchronization task. Nevertheless, only the left inferior parietal lobe (BA 40) posterior to the central sulcus, was active during the synchronize-listen comparison (column 1 of fig 5.4) at this threshold ($p < 0.001$). One of the important observations in PD patients was that syncopation resulted in activation at a much higher significance level than synchronization, to the extent that even at a corrected $p < 0.001$, several brain regions exhibited large clusters of activation (as can be seen in fig.5.4). Synchronization, on the other hand showed very little activation at this stringent threshold. However, when the threshold was lowered to a corrected $p < 0.01$, more brain regions typically associated with motor tasks were found to be active during synchronization (fig 5.5). Clusters of activation were found in the SMA, primary sensorimotor cortex, inferior parietal lobule (BA 40), superior frontal gyrus (BA 9), and bilateral cerebellum. It may be noted that the network of brain areas activated during synchronization is essentially a subset of brain areas that were activated during the syncopation task. A main effect of mode (fig.5.6) was observed only in the primary and secondary auditory areas (superior temporal and transverse temporal gyri, Heschl's gyrus - BA 41,42, 22) and reflected an increase in activity in these areas during the pacing tasks when the metronome was on, compared to the continuation tasks when the metronome was not present. The absence of a significant interaction between task and mode implied that the observed

differences between task conditions (synchronization and syncopation) occurred during both levels of mode (pacing and continuation) and vice versa.

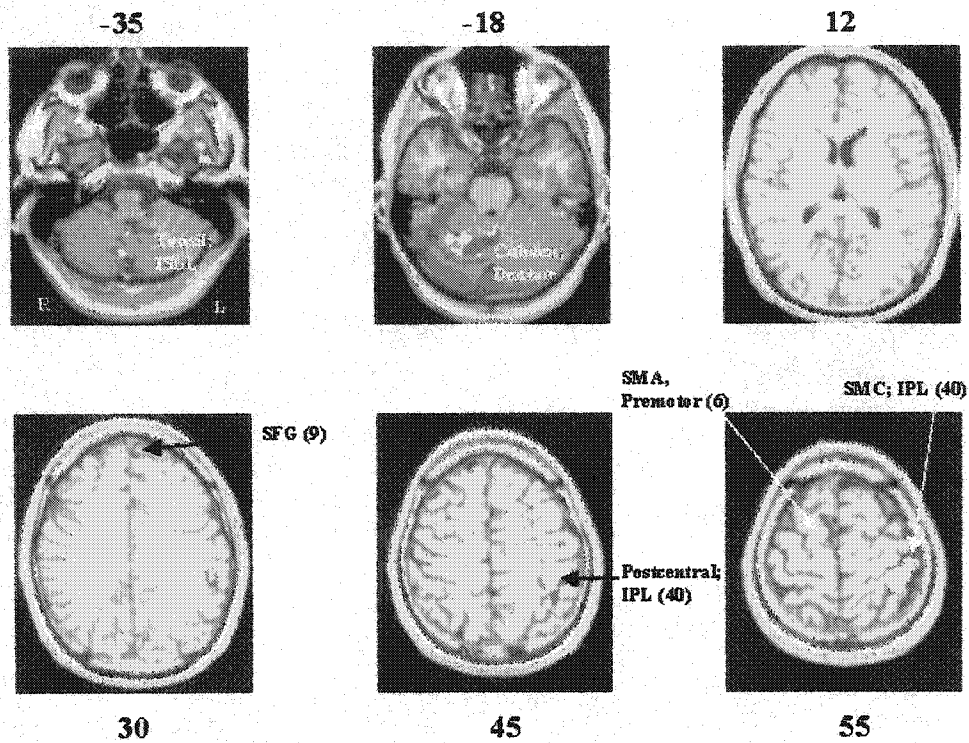


Fig. 5.5. Lowering the threshold to a significant level of $p < 0.01$ shows recruitment of more brain regions during the synchronization (Synchronize – Listen) task in Parkinson's disease patients. SFG – Superior Frontal Gyrus; IPL – Inferior Parietal Lobe; SMA – Supplementary Motor Area; SMC – Sensorimotor Cortex; ISLL – Inferior Semilunar Lobe of the cerebellum.

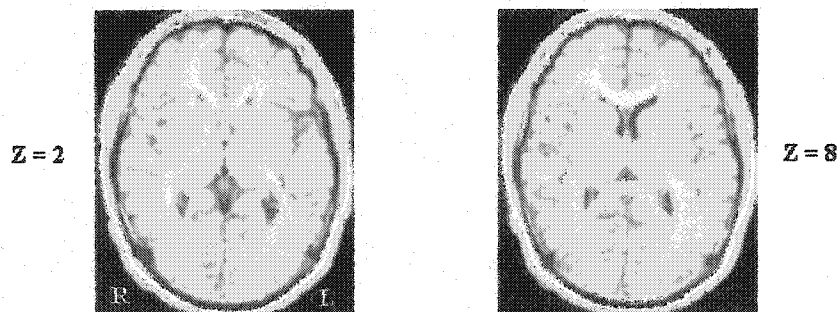


Fig. 5.6. The main effect of mode (Pace, Continue) in Parkinson's disease patients shows significant ($p < 0.01$) activation in bilateral auditory regions. (Superior Temporal and Transverse Temporal Gyri).

5.3.2.2. Age-matched control subjects

A 2-way ANOVA revealed only a main effect of task ($p < 0.01$) in control subjects, no main effect of mode and no significant interaction. Post-hoc tests done to characterize the contribution of different levels of task effects revealed more activation during syncopation (column 1 in fig.5.7) in bilateral sensorimotor cortex, bilateral premotor, SMA, left anterior cingulate (BA 24,32), right inferior parietal lobe, right insula and right primary and secondary auditory areas (STG, BA 41,42,22). A small cluster of activation was also observed in the right inferior semilunar lobule of the cerebellum. Additional sub-cortical areas such as the thalamus (Ventral Lateral Nucleus), putamen and lateral globus pallidus were also active during the syncopate task. Comparison of the syncopation and synchronization tasks in age-matched control subjects (second column of fig.5.7) however revealed activation of very few brain areas. This suggests similar activation patterns both during synchronization and syncopation. Brain activation during synchronization alone (synchronize minus listen) is not shown in fig.5.7, as the only area that was significantly active ($p < 0.05$) was the left sensorimotor cortex. The absence of a main effect of mode and interaction means that the differences in brain activation in control subjects during synchronization and syncopation persisted during both the pacing and continuation modes. The small subject pool of age-matched control subjects could have also contributed to a weak significance of results.

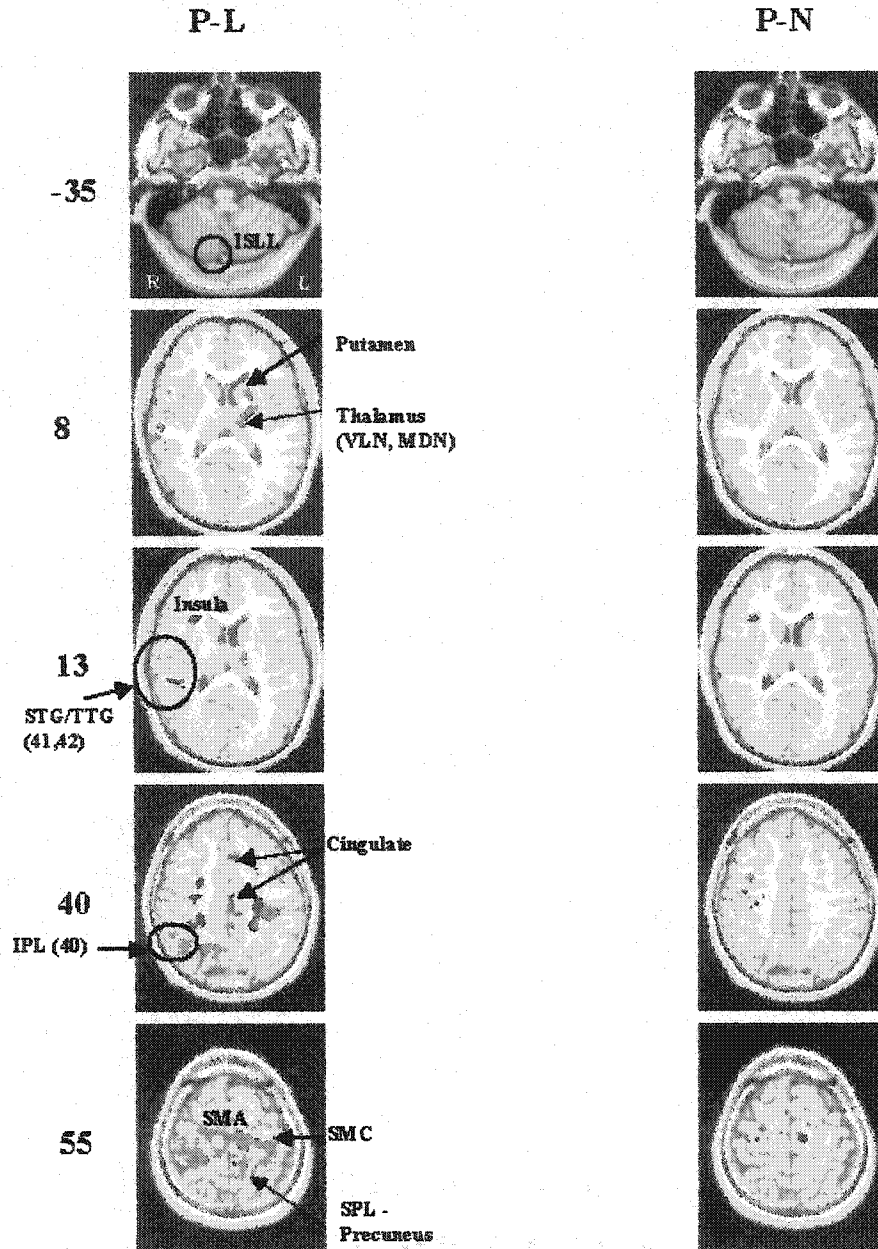


Fig. 5.7. Contribution of different task conditions to the main effect of task (Listen, Synchronize, Syncopate) in age-matched control subjects. The left column shows brain areas that were more active during syncopation compared to listening (N-L; $p < 0.01$) and the column to the right shows areas that were more active during syncopation compared to synchronization (P-N). VLN and MDN are the Ventral Lateral and Medial Dorsal Nuclei of the thalamus; STG / TTG are the primary and association auditory areas in the Superior Temporal and Transverse Temporal Gyri; IPL – Inferior Parietal lobe; SMA – Supplementary Motor Area; SMC – Sensorimotor Cortex; SPL – Superior Parietal Lobe.

5.4 DISCUSSION

This study provides insight into the neural basis of coordination and timing in Parkinson's disease patients and age-matched control subjects, using two well-established paradigms, the synchronization-syncopation paradigm of coordination dynamics and the continuation paradigm typically used in timing studies. To our knowledge this is the first fMRI study in Parkinson's disease patients to integrate the continuation paradigm with both modes of coordination. Results demonstrate that the pattern of recruitment of neural areas reflects not just the temporal and motor demands of the task, but also the way in which the required temporal interval is established to perform the task. Below, we discuss the imaging results in light of the differences observed between Parkinson's disease patients and control subjects (age-matched and young adults) and also in relation to the timing behavior corresponding to the two modes of coordination, i.e. synchronization and syncopation.

5.4.1. *Behavior*

From analysis of the behavioral performance, it is evident that both patients and age-matched controls are highly variable during the syncopation task and also during the continuation phase. Part of this difficulty may be attributed to the frequency of our auditory pacing tones (1.25 Hz) which both patients and age-matched control subjects reported as being fast. Almeida et al. (2002) examined Parkinson's disease patients using an in-phase and an anti-phase task at varying speeds (0.75 Hz, 1.25 Hz and 1.75 Hz) and found that patients were unable to coordinate limb movements to achieve the goal speeds as well as the control subjects. As the goal speed increased from 0.75 Hz

to 1.75 Hz, the performance of patients deteriorated in both tasks, more so in the anti-phase task. They hypothesized that the difficulties observed during anti-phase coordination in patients might be due to the deterioration in their ability to inhibit the tendency towards limb synchronization. Interestingly, Parkinson's disease patients exhibited more variability in IRI during paced syncopation than during continuing syncopation. Although this seems counter-intuitive, the following explanation seems plausible. Patients' behavioral data during syncopation show that their responses were more of a delayed reaction to the tones than proper syncopation. In fact, to make as good a syncopate response to each tone as possible they had to consciously avoid synchronizing to the tones and make a delayed response to each tone. If this were their strategy, they concentrated less on the duration between the tones and more on the time of occurrence of the tones. The tones, serving as auditory feedback may thus have interfered with the internal representation of duration and initiation of the motor response during paced syncopation, resulting in larger variability in IRI. However, since the tones were absent during continuation, there was no interference and patients in fact were able to maintain a mean IRI with less variability.

Recently our group conducted a similar fMRI experiment on young, right-handed adult subjects (N = 14) (Jantzen, Steinberg & Kelso, 2004). Table 5.3 allows a quick comparison of behavioral results among the three groups of subjects – PD patients, age-matched controls and young adults. One of the striking differences between the earlier study and the current one is the ability of young adults to accurately perform the syncopation task compared to the subjects in this study. The mean relative phase

during the syncopation task was $187.9^0 \pm 50.7^0$ (mean \pm SD) and there was no significant difference in variability of relative phase between synchronize and syncopate conditions. Parkinson's disease patients slowed down during continuation (irrespective of synchronization or syncopation) compared to young adults who were able to keep the same pace (IRI) during continuation. However, young adults slowed down during the syncopation task compared to synchronization. The difficulty that PD patients experienced in performing these tasks is reflected by the variability of IRI compared to control subjects. Even after a temporal interval is initiated using pacing tones, PD patients seem to have difficulty in maintaining the pace - at least in translating this temporal information into motor responses. The main difficulty for age-matched controls seems to be timing demands of the syncopation task. They are able to continue once paced by auditory tones. Hence, this behavioral data suggests that the difficulty that PD patients experienced in syncopation over synchronization could possibly not be entirely due to the disease process but partly be age-related, while that in continuation (over pacing) may be disease-related. Analysis of data according to Wing-Kristofferson model allowed us to examine whether the motor or clock variance is affected in PD patients and controls. However, data did not reveal any significant difference between these parameters during continuation of synchronization and syncopation tasks in PD patients or young adults.

Analysis	PD patients	Age-matched controls	Young adults*
Relative phase (Mean \pm SE) during paced syncopation	37.65 \pm 33.9	57.86 \pm 45.3	189.7 \pm 13.5
t-test – variability of relative phase between paced synchronize (N) and syncopate (P)	P > N (p<0.00095)	P > N (p<0.02)	No significant difference
Mean IRI	Pace faster than Continue	P faster than N	N faster than P
2-way ANOVA on IRI	Main effect of mode only (Pace faster than Continue)	No significant effects	Main effect of task only (N faster than P)
2-way ANOVA on variability (SD) of IRI	Main effect of task (P > N); Main effect of mode (Pace > continue); No interaction	Main effect of task only (P > N)	No significant difference
Wing and Kristofferson – Motor and Clock variance during continuation of N and P	No significant difference	Not done	No significant difference

* Jantzen, Steinberg & Kelso, 2004

Table 5.3. Comparison of behavioral data among three groups of subjects – PD patients, age-matched controls and young adults.

5.4.2. Brain Activation

5.4.2.1. Pacing Vs. Continuation

In our study, although Parkinson's disease patients showed a significant slowing of their responses during continuation (larger IRI) following both synchronization and syncopation, brain activation during pacing and continuation were quite similar except for additional activation in bilateral primary and secondary auditory areas during pacing. In an fMRI study on adult healthy individuals, Jäncke et al. (2000) found a similar pattern of activation during pacing and continuation, but they failed to observe any significant difference between the two phases of synchronization. Another study by Rao et al. (1997) found additional activity in motor areas such as

SMA, putamen and insula and in the superior temporal and inferior frontal gyri during continuation. They surmised that activation in the right superior temporal and inferior frontal gyri suggested involvement of a loop, which is specifically associated with retrieval and rehearsal of auditory information, particularly in the absence of an auditory stimulus. No such loop was significantly active in control subjects or patients in our study when pacing was compared with continuation.

5.4.2.2. Neural activation in young adults

Data analysis quite similar to that done in this paper yielded the following results in young adults (Jantzen, Steinberg & Kelso, 2004). Bilateral auditory areas were more active during pacing compared to continuation. The syncopation task revealed more activation in the SMA, middle frontal gyrus, superior parietal lobe, middle temporal gyrus, striatum, Ventral Posterior Lateral nucleus of the thalamus and cerebellum. Interestingly, the pattern of activation during the pacing phase of both coordination modes (synchronization and syncopation) persisted during their respective continuation phases. The main difference in activation from elderly controls scanned here is the absence of activation in the anterior cingulate, inferior parietal lobe and insula. It seems that a smaller network of brain areas is recruited in young adults to execute the same task. This supports the fact that age-related compensatory mechanisms tend to activate brain areas over and above those regions that are normally activated.

5.4.2.3. Activation in Parkinson's disease patients and age-matched control subjects

Differences in activation between synchronization and syncopation and their respective continuation phases cannot be explained by different behavioral parameters, since both tasks require subjects to generate a series of isochronous responses at the same interval. Hence the observed differences most likely resulted from inherent differences in the cognitive demands of the task and differential representation of temporal information. The syncopation task requires subjects to maintain an anti-phase relationship, imposes greater cognitive and attentional demands (Meyer-Lindenberg et al., 2002; Monno et al., 2002) and is a less stable coordination mode than synchronization (Kelso et al., 1990; 1992; 2001). This resulted in a wider network of brain activation during syncopation than synchronization (Jantzen et al., 2001; Mayville et al., 2002; Meyer-Lindenberg et al., 2002) in both Parkinson's disease patients and age-matched controls. Activation during syncopation in age-matched subjects is very similar to that reported in young adults (Jantzen, Steinberg & Kelso, 2004; Mayville et al., 2002) with additional activation in the insula and inferior parietal lobe in age-matched controls. The idea behind including age-matched controls in this study was to distinguish the effects of Parkinson's disease from those due to aging. Previous research has shown that age affects anti-phase coordination, but not in-phase movements (Wishart et al., 2000; Greene & Williams 1996). In addition, the availability of dopamine D1 and D2 receptor groups and dopamine transporter protein density in the human striatum declines every decade (Kaasinen & Rinne, 2002) and has been purported to be responsible for some of the cognitive decline related to aging. Similar rates of age-

related decline occur in the cortex (faster in the frontal cortex compared to the temporal lobe) and the thalamus. Evidently, elderly control subjects compensate for age-related losses or decline in neural function in order to achieve comparable behavioral output as young adults. Hence the additional neural activation seen in these subjects might reflect the extra working memory and attentional resources needed for making an anti-phase response during syncopation. Below we discuss the possible functional role of the extra neural activation observed during syncopation than synchronization seen in Parkinson's disease patients and control subjects.

5.4.3. Basal Ganglia

Activation in the basal ganglia is of interest in studies involving Parkinson's disease patients as dopaminergic levels are depleted in these nuclei and one would expect to find no or minimal basal ganglia activation during coordination tasks. The activation that we observed in the basal ganglia may have resulted from the fact that the patients were on medication. Much of the previous results on the involvement of basal ganglia in Parkinson's disease (Harrington et al., 1998; O'Boyle et al., 1996; Pastor et al., 1992) have demonstrated that although patients are able to reproduce a given temporal interval, variability is significantly enhanced. These results have been interpreted within the framework of Wing and Kristofferson's (1973) timing model that assumes that the basal ganglia acts as an internal clock whose variance is independent of motor implementation. The role of the basal ganglia as an internal clock is further supported by previous research (Arteida et al., 1992; Harrington et al., 1998; Pastor et al., 1992) demonstrating that Parkinson's disease patients exhibit

diminished time perception abilities. It is interesting to note that our results in Parkinson's disease patients (and recent findings on young adults – Jantzen, Steinberg & Kelso, 2004) show significant basal ganglia activity only during syncopation. Since the motor demands of both the tasks are identical and they differ mostly in their timing requirements, activation in the basal ganglia points to its role in timing as demanded by the syncopation task. An alternate interpretation to the role of basal ganglia is its involvement in executing seemingly difficult tasks. Boecker et al. (1998) reported increasing blood flow to the SMA and associated pallido-thalamic loops, when subjects performed an increasingly complex sequence of movements. Similarly Rao et al. (1997) found basal ganglia activation only during the continuation phase of synchronization (not during pacing). Although convincing evidence for a role of the basal ganglia in timing and execution of movements exists, a role in timing per se cannot be attributed to basal ganglia from the results of this study, as no activation was observed during the synchronization task. However, basal ganglia activation occurs when the task entails difficult cognitive abilities or strategies in translating the temporal information into movement patterns, as in the case of syncopation.

5.4.4. Cerebellum

Although there is no evidence of cerebellar deficiency in Parkinson's disease, activation in the cerebellum becomes important from the timing perspective (Penhune et al., 1998; Mangels et al., 1998; Kawashima et al., 2000; Ivry & Richardson, 2002). Patients with cerebellar lesions show impairment in rhythmic tapping tasks and continuation tasks (Ivry et al., 1988; Ivry & Keele 1989). The lateral cerebellum

consists of the dentate nucleus, the dorsal and ventral parts of which project into the premotor cortex and the dorsolateral prefrontal cortex, such that time keeping operations could directly involve neural systems involved in sensorimotor processing and working memory. In contrast, the medial cerebellum projects to the spinal cord, directly impacting muscle activity and thereby affecting motor implementation (Harrington & Haaland, 1999). Our data show that Parkinson's disease patients had extensive activation in the cerebellum than age-matched controls during both coordination tasks, more so during syncopation. Stronger activation during syncopation may result from the larger timing requirements of that task compared to synchronization.

5.4.5. Cortical areas

Among all areas of activation observed in Parkinson's disease patients during syncopation, the most prominent cluster is that which extends posteroinferiorly from the primary sensorimotor cortex to the superior and inferior parietal lobes (BA 40). Several previous PET studies on timing using rhythm discrimination (Roland et al., 1981), time bisection procedures (Maquet et al., 1996), synchronous tapping (Lejeune et al., 1997) and an event-related fMRI study using a time-discrimination task (Rao et al., 2001), have found significant activation in the parietal cortex of normal adults. Although the parietal cortex receives no direct input from the basal ganglia it has reciprocal connections with the SMA, premotor and prefrontal cortex (Pandya & Yeterian, 1985). The parietal cortex projects to the cerebellum through the premotor cortex and pontine nuclei (Schmahmann & Pandya, 1989) and receives cerebello-

thalamocortical projections too (Schmahmann & Pandya, 1990). Further anatomical evidence for incriminating the parietal cortex in timing comes from monkey studies where it was shown - using anterograde tracers injected at the inferior parietal lobe, that the inferior parietal cortex has topographic projections to the putamen and caudate nucleus (Cavada & Goldman-Rakic, 1991). Since each parietal subdivision is part of a distinct distributed corticocortical network, this observation suggests the existence of functional specialization of different parts of the striatum. With intricate connections to the basal ganglia and cerebellum, it is plausible that the parietal cortex is involved in timing. Clinical observations also suggest that the left parietal cortex plays a role in timing. Patients with limb apraxia following lesions of the left parietal cortex, typically have difficulty in timing gestures. Right parietal lesions on the other hand result in neglect, suggesting that attentional operations could support timing. Several studies in Parkinson's disease patients using simple motor tasks have demonstrated overactivity in the parietal cortex in addition to SMA and premotor cortex (Rascol et al., 1997; Samuel et al., 1997; Sabatini et al., 2000; Haslinger et al., 2001). Authors of most of these studies argue that in Parkinson's disease, there is a switch from the use of the defective striato-mesial frontal pathway to the relatively intact parietal-lateral premotor circuits in order to facilitate the performance of complex movements. The parietal cortex acts as an integrator of different sensory, motivational and attentional inputs to provide sensory-guided movement in the absence of an intact basal ganglia-mesial frontal system. Activation of the cerebellar-parietal-premotor loop may also represent a compensatory mechanism to bypass the defective striato-frontal circuit.

Activation in the SMA in Parkinson's disease patients requires careful consideration for two reasons. First, the major dorsal putamen output is to the SMA (Alexander et al., 1990) and then to different cortical areas. Second, previous functional imaging studies (Playford et al., 1992; Rascol et al., 1992; Samuel et al., 1997; Sabatini et al., 2000; Haslinger et al., 2001) have found a reduced activation especially in the rostral SMA, which receives projections from the putamen. The defective SMA activation is thought to reflect the decrease in positive feedback arising from the basal ganglia-thalamocortical motor loop due to striatal dopamine depletion. Further studies revealed that this underactivity occurred mainly when the movement or its timing was chosen by the subjects themselves (Catalan et al., 1999) and was reversible with L-DOPA therapy (Haslinger et al., 2001), pallidotomy (Grafton et al., 1995) and stimulation of the subthalamic nucleus (Ceballos-Baumann et al., 1999). In our study, SMA activation was noticed to varying degrees in all task conditions in patients and both groups of control subjects. It is likely that part of the basal ganglia-thalamocortical insufficiency was compensated for, since our patients were tested while on medication. The greater activation of SMA during syncopation is consistent with the role of this area in motor preparation because syncopation involves planning and executing responses on a cycle-by-cycle basis compared to synchronization, which is done as an automatic task once the pattern is established (Mayville et al., 2002). Significant activation of the mid-dorsal and dorsolateral prefrontal cortex during the syncopation task in patients may reflect the higher cognitive demands of the task (attention and working memory), as the role of these areas in the organization of motor behavior is generally thought to relate to attention and working memory.

5.5. Summary and Conclusions

Our study clearly shows that functionally and anatomically discrete networks subserve timing in different contexts. Behavioral (Rammsayer & Lima, 1991) and pharmacological (Rammsayer, 1993; 1999) studies have previously provided evidence that different timing systems operate in the milliseconds and seconds range. Following a comprehensive review of the neuroimaging literature, Lewis & Miall (2003) conclude that there is evidence to support the existence of at least two distinct neural systems for the control of timing - one is relatively automatic and acts primarily on short time scales and the other is under cognitive control and active for longer duration, non-motor tasks. Differential neural activation during synchronization and syncopation in our study may reflect the recruitment of two distinct processing networks. Since differences in brain activity during paced synchronization and syncopation persisted during their respective continuation phases, we conclude that the network engaged to process temporal information depends not only on constraints imposed by temporal factors, but on context as well (Jantzen, Steinberg & Kelso, 2002b; 2004). Although most popular process models of interval timing propose the existence of specific mechanisms for representing and storing temporal intervals (Creelman, 1962; Treisman, 1963; Church, 2003), little is known about their specific neural representation. Based on our results (supported by Jantzen, Steinberg & Kelso, 2002b; 2004), we propose that the pattern of neural activity is defined by at least the following two mechanisms – 1) the specific sensorimotor and timing information (duration) required for accurate performance of the task determines the timing network to be activated 2) the nature of the temporal

task as defined by context, decides the pattern of connectivity or communication between cortical and subcortical regions. Once this pattern of activation has been established, the same brain areas remain active, as long as the temporal information continues to be referenced.

Age-related changes in brain activation are more pronounced when subjects perform the difficult syncopation task. More activation in the anterior cingulate and sensorimotor integration areas such as the insula and inferior parietal cortex in age-matched controls compared to young adults concerns the attention and sensorimotor integration necessary to link decision-making processes with task execution. To compensate for the functional deficiency in Parkinson's disease, patients recruit functionally segregated circuits that connect the striatum and association areas of the parietal, premotor and prefrontal cortices. Further studies into the biochemical modulation of these dopaminergic pathways by alternate connectivities (task and context-dependent) will help us understand these compensatory mechanisms in Parkinson's disease better.

Chapter 6

General Discussion

6.1. Evidence for a principle of brain function

This dissertation aimed at understanding the neural correlates of motor coordination and music perception using functional MRI. The basic questions were explored in a set of four experiments. It is clear from these studies that the brain engages multiple cortical and cerebellar structures to varying degrees for planned goal-directed action. Depending on the cognitive demands of the task as well as context, some of these areas are coupled and decoupled into the network for task execution. In our studies on stroke and Parkinson's disease, we found evidence for a different pattern of neural activation compared to that observed in healthy adults. This provides evidence for plasticity in the brain in order to compensate for functional insufficiencies. Differential neural recruitment in trained musicians and non-musicians while listening to music attests to the fact that functional connectivity is also determined by the subjects' previous experience and cognitive state. In other words, the way different brain regions talk to each other, within and across hemispheres, is shaped not only by their anatomical connections, but also by how previous experience affects the strengths of these connections. The influence of local and global connections on brain regions involved in goal-directed action seems to be modulated by several cognitive processes such as attention, memory and intention that define the overall "cognitive state and cognitive policy". Collectively, our studies point to the brain as a

highly interconnected, spatiotemporal dynamical system that uses distributed representational schemes. These representations define behavior and behavior in turn moulds representations based on contextual demands. Presenting evidence for the existence of the above principles in the human brain using functional MRI is a major contribution of this dissertation.

6.2. General summary and implications

We started with a detailed description of the events at the neural level that contribute to the BOLD response. This understanding is crucial for an accurate interpretation of the BOLD response since it depends on neural activity and blood flow dynamics. In the finger-sequencing study in normal healthy adults, we identified the neural substrates of goal-directed action. We found evidence that similar neural networks are engaged for execution and imagination of movement sequences. Interestingly, we also found that the sensorimotor cortical and cerebellar areas are functionally decoupled from the task network when people imagine but do not actually execute sequential actions. This strongly suggested that only intended and realized action sequences engage this hypothesized cortico-cerebellar loop. We also demonstrated that parietal cortex is especially engaged in difficult spatial tasks that that rely on remembering and executing the correct ordering of task components.

In chapter 3, we found differentiation and compensatory processes during recovery from stroke. Using imagery tasks, we showed that hemiplegic patients retained the

ability to activate neural pathways that are normally involved in executing goal-directed action sequences, despite the loss of ability to actually execute movements. This points to the possible rehabilitative potential for such tasks. What was quite surprising was the fact that the functionally dormant pathways were triggered nine months after the neurological insult using treatment methods outlined in the study and fMRI can capture those changes over time. Although the recovery mechanisms in each individual may depend to a large extent on the nature and location of the lesion, our study showed evidence that these processes involve the cooperative action of several cortical regions within and even across hemispheres. Identifying a proper task to trigger the dormant motor pathways is also crucial in formulating a treatment protocol for functional recovery from stroke.

One of the interesting observations in our music study was activation in the limbic and paralimbic areas in both musicians and non-musicians while listening to expressive music. Most likely, this points to the aesthetic and affective experience while listening to music. The implication of this finding however, is not limited to evidence that listening to expressive music can be an aesthetic experience. Limbic activation may also represent the motivational aspect of expressive music. It makes us wonder whether limbic activation could directly relate to the improvement in motor function that is observed in people with motor deficits when they listen to music. For the first time using fMRI, we were able to provide evidence for the existence of shared neural resources for processing of music and language - a finding that may help ethnomusicologists and evolutionary psychologists formulate a common basis for the communication of meaning in music and language.

In our study on timing and motor coordination in Parkinson's disease patients, we found evidence for recruitment of specific neural networks for two modes of coordination. The pattern of activity seems to be defined by at least two processes – first, the specific sensorimotor and timing information (duration) required for accurate performance of the task determines the timing network to be activated; second, the nature of the temporal task as defined by context, decides the pattern of connectivity or communication between cortical and subcortical regions. Once this pattern of activation has been established, the same brain areas remain active, as long as the temporal information continues to be referenced. In order to compensate for the functional deficiency in Parkinson's disease, patients recruit functionally segregated circuits that connect the striatum and association areas of the parietal, premotor and prefrontal cortices. This activity is specific to patients and is not seen in age-matched control subjects or young adult subjects.

6.3. Future work

Identifying brain regions involved in tasks that we used is just the first step towards getting a better picture of brain mechanisms in motor coordination. Given the modulatory influences of cognitive phenomena such as attention, memory and intention on the pattern of neural activation, it is desirable that one correlates activation with behavioral data. The actual time-dependence of neural processes cannot be assessed using fMRI alone. However, in conjunction with multi-channel MEG and EEG recordings, deeper insights into the spatiotemporal dynamics of the

human brain may well emerge. The idea behind this dissertation work does not end with identification of these areas nor by providing evidence for cooperative action of brain areas to produce goal-directed action. Further investigation into the neurochemistry of brain areas will go a long way in better understanding the communication between neural regions. We have started a study using fluoro-DOPA PET to relate these neural activations in Parkinson's disease patients to the dopaminergic status of different neural areas. Having a better idea about the distribution of the dopaminergic deficiency will help us answer some questions about cognitive decline in Parkinson's disease. Similarly in stroke patients, it is desirable to do flow-related studies to identify vasoreactivity following stroke. Combined with functional imaging data, this provides clues to the nature of functional recovery following stroke. Although music therapy is being used widely in many hospitals and institutions across the world for improving the quality of life of patients, careful analysis of what music does to improve function – for instance how listening to music affects blood flow responses, neural activation threshold, blood biochemistry etc, would go a long way in scientifically interpreting these effects. The benefits of such research is not limited to motor disorders per se, but has overarching implications on the treatment of communication and behavioral disorders as well.

References

- Akopov, S., & Whitman, G.T. (2002). Hemodynamic studies in early ischemic stroke: serial transcranial Doppler and magnetic resonance angiography evaluation. *Stroke*, 33(5), 1274-1279.
- Alexander, G.E., Crutcher, M.D., & DeLong, M.R. (1990). Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. *Progress in Brain Research*, 85, 119-146.
- Alexander, G.E., DeLong, M.R., & Strick, P.L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Reviews in Neuroscience*, 9, 357-381.
- Alexandrov, A.V., Demchuk, A.M., Wein, T.H., & Grotta, J.C., (1999). Yield of transcranial Doppler in acute cerebral ischemia. *Stroke*, 30(8), 1604-1609.
- Almeida, Q.J., Wishart, L.R., & Lee, T.D. (2002). Bimanual coordination deficits with Parkinson's disease: the influence of movement speed and external cueing. *Movement Disorders*, 17(1), 30-37.
- Arthurs, O.J., & Boniface, S. (2002). How well do we understand the neural origins of the fMRI BOLD signal? *Trends in Neurosciences*, 25(1), 27-31.
- Artieda, J., Pastor, M.A., Lacruz, F., & Obeso, J.A. (1992). Temporal discrimination is abnormal in Parkinson's disease. *Brain*, 115 Pt 1, 199-210.
- Attwell, D., & Iadecola, C. (2002). The neural basis of functional brain imaging signals. *Trends in Neurosciences*, 25(12), 621-5.
- Attwell, D., & Laughlin, S.B. (2001). An energy budget for signaling in the gray matter of the brain. *Journal of Cerebral Blood Flow and Metabolism*, 21(10), 1133-45.

- Bahn, M.M., Oser A.B., & Cross, D.T. (1996). CT and MRI of acute stroke. *Journal of Magnetic Resonance Imaging*, 6, 833-845.
- Baird, A.E., & Warach, S. (1998). Magnetic resonance imaging of acute stroke. *Journal of Cerebral Blood Flow and Metabolism*, 18(6), 583-609.
- Bakker, D., & Pauwels, E.K. J. (1997). Stroke: the role of functional imaging. *European Journal of Nuclear Medicine*, 7; 24, 2-5.
- Balkwill, L-L., & Thompson, W.F. (1999). A cross-cultural investigation of the perception of emotion in music: Psychophysical and cultural cues, *Music Perception*, 17(1), 43-64.
- Bandettini, P.A. (2000). The temporal resolution of functional MRI. In Moonen, C.T.W. and Bandettini, P.A., (Eds.), *Functional MRI*, Springer Verlag.
- Bechara, A., Tranel, D., Damasio, H., & Damasio, A.R. (1996). Failure to respond autonomically to anticipated future outcomes following damage to prefrontal cortex. *Cerebral Cortex*, 6(2), 215-25.
- Bellgowan, P.S., Saad, Z.S., & Bandettini, P.A. (2003). Understanding neural system dynamics through task modulation and measurement of functional MRI amplitude, latency, and width. *Proceedings of the National Academy of Sciences of the United States of America*, 100(3), 1415-9.
- Bever, T.G. & Chiarello, R.J. (1974). Cerebral dominance in musicians and non-musicians. *Science*, 185, 537-539.
- Binder, J.R., Frost, J.A., Hammeke, T.A., Bellgowan, P.S.F., Rao, S.M. & Cox, R.W. (1999). Conceptual processing during the conscious resting state, A functional MRI study. *Journal of Cognitive Neuroscience*, 11, 80-93.
- Binkofski, F., Buccino, G., Posse, S., Seitz, R.J., Rizzolatti, G., & Freund. H-J. A. (1999). A fronto-parietal circuit for object manipulation in man: evidence from an fMRI-study. *European Journal of Neuroscience*, 11, 3276-3286.

- Bittar, P.G., Charnay, Y., Pellerin, L., Bouras, C., & Magistretti, P.J. (1996). Selective distribution of lactate dehydrogenase isoenzymes in neurons and astrocytes of human brain. *Journal of Cerebral Blood Flow and Metabolism*, 16(6), 1079-89.
- Blood A.J., & Zatorre R.J. (2001). Intensely pleasurable responses to music correlate with activity in brain regions implicated in reward and emotion. *Proceedings of the National Academy of Sciences of the United States of America*, 98 (20), 11818–11823.
- Blood, A.J., Zatorre, R.J., Bermudez, P. & Evans, A.C. (1999). Emotional responses to pleasant and unpleasant music correlate with activity in paralimbic brain regions, *Nature Neuroscience*, 2 (4), 382-387.
- Boecker, H., Dagher, A., Ceballos-Baumann, A.O., Passingham, R.E., Samuel, M., Friston, K.J., Poline, J., Dettmers, C., Conrad, B., & Brooks, D.J. (1998). Role of the human rostral supplementary motor area and the basal ganglia in motor sequence control: investigations with H2 15O PET. *Journal of Neurophysiology*, 79(2), 1070-1080.
- Boynton, G.M., Engel, S.A., Glover, G.H., & Heeger, D.J. (1996). Linear Systems Analysis of Functional Magnetic Resonance Imaging in Human V1. *Journal of Neuroscience*, 16(13), 4207–4221.
- Buchkremer-Ratzmann, I., August, M., Hagemann, G., & Witte, O.W. (1996). Electrophysiological transcortical diaschisis after cortical photothrombosis in rat brain. *Stroke*, 27, 1105-1109.
- Buckner, R.L. (2003). The hemodynamic inverse problem: Making inferences about neural activity from measured MRI signals. *Proceedings of the National Academy of Sciences of the United States of America*, 100(5), 2177-9.
- Buckner, R.L., Bandettini, P.A., O'Craven, K.M., Savoy, R.L., Petersen, S.E., Raichle, M.E., & Rosen, B.R. (1996). Detection of cortical activation during averaged single trials of a

- cognitive task using functional magnetic resonance imaging. *Proceedings of the National Academy of Sciences of the United States of America*, 93(25), 14878-83.
- Bush, G., Luu, P., & Posner, M.I. (2000). Cognitive and emotional influences in anterior cingulate cortex, *Trends in Cognitive Sciences*, 4(6), 215-222.
- Buxton, R.B. (2001). The elusive initial dip. *Neuroimage*, 13(6 Pt 1), 953-8.
- Cabeza, R., & Nyberg, L. (2000). Imaging cognition II: An empirical review of 275 PET and fMRI studies. *Journal of Cognitive Neuroscience*, 12(1), 1-47.
- Calautti, C., Leroy, F., Guineestre, J.Y., & Baron, J.C. (2001). Dynamics of motor network overactivation after striatocapsular stroke: a longitudinal PET study using a fixed-performance paradigm. *Stroke*, 32, 2534-2542.
- Carson, R.G., Chua, R., Byblow, W.D., Poon, P., & Smethurst, C.J. (1999). Changes in posture alter the attentional demands of voluntary movement. *Proceedings of the Royal Society of London. Series B. Biological sciences*, 266(1421), 853-857.
- Carter, C.S., Braver, T.S., Barch, D.M., Botvinick, M.M., Noll, D. & Cohen, J.D. (1998). Anterior Cingulate cortex, Error detection and online monitoring of performance, *Science*, 280, 747-749.
- Catalan, M.J., Ishii, K., Honda, M., Samii, A., & Hallett, M. (1999). A PET study of sequential finger movements of varying length in patients with Parkinson's disease. *Brain*, 122 (Pt 3), 483-495.
- Cavada, C., & Goldman-Rakic, P.S. (1991). Topographic segregation of corticostriatal projections from posterior parietal divisions in the macaque monkey. *Neuroscience*, 42, 683-696.
- Ceballos-Baumann, A.O., Boecker, H., Bartenstein, P., von Falkenhayn, I., Riescher, H., Conrad, B., Moringlane, J.R., & Alesch, F. (1999). A positron emission tomographic study of subthalamic nucleus stimulation in Parkinson disease: enhanced movement-related activity

- of motor-association cortex and decreased motor cortex resting activity. *Archives of Neurology*, 56(8), 997-1003.
- Chlan, L., & Tracy, M.F. (1999). Music therapy in critical care: indications and guidelines for intervention, *Critical care nurse*, 19(3), 35-41.
- Chollet, F., DiPiero, V., Wise, R.J., Brooks, D.J., Dolan, R.J., & Frackowiak, R.S. (1991). The functional anatomy of motor recovery after stroke in humans: a study with positron emission tomography. *Annals of Neurology*, 29, 63-71.
- Church, R.M. (2003). A concise introduction to scalar timing theory. 3-22.
- Clark, M.E., Lipe, A.W., & Bilbrey, M. (1998). Use of music to decrease aggressive behaviors in people with dementia, *Journal of gerontological nursing*, 24(7), 1-7.
- Clark, V.P., Maisogm J.M., & Haxby, J.V. (1998). fMRI study of face perception and memory using random stimulus sequences. *Journal of Neurophysiology*, 79(6), 3257-65.
- Clarke, S., Bellmann Thiran, A., Maeder, P., Adriani, M., Vernet, O., Regli, L., Cuisenaire, O., & Thiran, J.P. (2002). What and where in human audition: selective deficits following focal hemispheric lesions. *Experimental Brain Research*, 147(1), 8-15.
- Cooper, J.A., Sagar, H.J., & Sullivan, E.V. (1993). Short-term memory and temporal ordering in early Parkinson's disease: effects of disease chronicity and medication. *Neuropsychologia*, 31(9), 933-49.
- Cox, R.W, & Jesmanowicz, A. (1999). Real-time image registration for functional MRI. *Magnetic Resonance in Medicine*, 42, 1014-1018.
- Cox, R.W. (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research, an International Journal*, 29, 162-173.

- Cramer, S.C. (1999). Stroke recovery: lessons from functional MR imaging and other methods of human brain mapping. *Physical medicine and rehabilitation clinics of North America*, 10(4), 875-886.
- Cramer, S.C., & Bastings, E.P. (2000). Mapping clinically relevant plasticity after stroke. *Neuropharmacology*, 39, 842-851.
- Cramer, S.C., Nelles, G., Benson, R.R., Kaplan, J.D., Parker, R.A., Kwong, K.K., Kennedy, D.N., Finklestein, S.P., & Rosen, B.R. (1997). A functional MRI study of subjects recovered from hemiparetic stroke. *Stroke*, 28, 2518-2527.
- Crammond, D.J. (1997). Motor imagery: never in your wildest dreams. *Trends In Neurosciences*, 20, 54-57.
- Creelman, C.D. (1962). Human Discrimination of Auditory Duration. *The Journal of the Acoustical Society of America*, 34, 582-593.
- Creutzfeldt, O. (1975). Brain work: The coupling of function, metabolism and blood flow in the brain. Ingvar, D. and Lassen, N.A. (Eds.) *Alfred Benzon symposium VIII*, Munksgaard, Copenhagen.
- Dale, A.M., & Buckner, R.L. (1997). Selective averaging of rapidly presented individual trials using fMRI. *Human Brain Mapping*, 5, 329-340.
- Damasio, A.R. (1996). The somatic marker hypothesis and the possible functions of the prefrontal cortex. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, 351(1346), 1413-20.
- Dassonville, P., Lewis, S.M., Zhu, X.H., Ugurbil, K., Kim, S-G. & Ashe. J. (1998). Effects of movement predictability on cortical motor activation. *Neuroscience Research*, 32, 65-74.
- Davis, S., Tress, B., Barber, P.A., Darby, D., Parsons, M., Gerraty, R., Yang, Q., Donnan, G., & Desmond, P. (2000). Echoplanar magnetic resonance imaging in acute stroke. *Journal of Clinical Neuroscience*, 7(1), 3-8.

- Deiber, M.P., Honda, M., Ibanez, V., Sadato, N., & Hallett, M. (1999). Mesial motor areas in self-initiated versus externally triggered movements examined with fMRI: effect of movement type and rate. *Journal of Neurophysiology*, 81, 3065-3077.
- Deiber, M.P., Ibanez, V., Honda, M., Sadato, N., Raman, R., & Hallett, M. (1998). Cerebral processes related to visuomotor imagery and generation of simple finger movements studied with positron emission tomography. *Neuroimage*, 7, 73-85.
- Devinsky, O., Morrell, M.J., & Vogt, B.A. (1995). Contributions of anterior cingulate cortex to behavior. *Brain*, 118 (Pt 1), 279-306.
- Di Piero, V., Chollet, F.M., MacCarthy, P., Lenzi, G.L., & Frackowiak, R.S.J. (1992). Motor recovery after acute ischemic stroke, a metabolic study. *Journal of Neurology Neurosurgery and Psychiatry*, 55, 990-996.
- Duong, T.Q., Kim, D.S., Ugurbil, K., & Kim, S-G. (2001). Localized cerebral blood flow response at submillimeter columnar resolution. *Proceedings of the National Academy of Sciences of the United States of America*, 98(19), 10904-9.
- E. Mellet, L. Petit, B. Mazoyer, M. Denis, N. Tzourio, Reopening the mental imagery debate: Lessons from functional anatomy. *Neuroimage*, 8, 129-139.
- Edelman, G.M., & Tononi, G. (2000). *A universe of consciousness: How matter becomes imagination*, Basic books.
- Ellerman, J.M., Flament, D., Kim, S.G., Fu, Q.G., Merkle, H., Ebner, T.J., & Ugurbil, K. (1994). Spatial patterns of functional activation of the cerebellum investigated using high field (4T) MRI. *NMR in Biomedicine*, 7, 63-68.
- Fahn, S., Eltin, R., & members of the UPDRS development committee. (1987). Unified Parkinson's Disease Rating Scale. In: Fahn, S., Marsden, C.D., Goldstein, M., Calne, D.B. eds. *Recent development in Parkinson's disease*. Macmillan: New York.
- Feeney, D.M., & Baron, J.C. (1986). Diaschisis. *Stroke*, 17, 817-830.

- Fisher M, Prichard J.W., & Warach, S. (1995). New magnetic resonance techniques for acute ischemic stroke. *JAMA- the journal of the American Medical Association*, 274(11), 908-911.
- Fox, P.T., & Raichle, M.E. (1986). Focal physiologic uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. *Proceedings of the National Academy of Sciences of the United States of America*, 83, 1140-1144.
- Fox, P.T., Raichle, M.E., Mintun, M.A., & Dence, C. (1988). Non-oxidative glucose consumption during focal physiologic neural activity. *Science*, 241, 462-464.
- Frackowiak, R.S.J., & Lammertsma, A.A. (1985). Clinical measurement of cerebral blood flow and oxygen consumption. In: Reivich M, Alavi, A. eds. *Positron Emission Tomography*, New York, Wiley-Liss, 153-181.
- Frahm, J., Merboldt, K.D., Hanicke, W., Kleinschmidt, A., & Boecker, H. (1994). Brain or vein-oxygenation or flow? On signal physiology in functional MRI of human brain activation. *NMR in Biomedicine*, 7(1-2), 45-53.
- Fries, P., Reynolds, J.H., Rorie, A.E., & Desimone, R. (2001). Modulation of oscillatory neuronal synchronization by selective visual attention. *Science*, 291(5508), 1560-3.
- Fries, W., Danek, A., Scheidtmann, K., & Hamburger, C. (1993). Motor recovery following capsular stroke: role of descending pathways from multiple motor areas. *Brain*, 116, 369-382.
- Friston, K.J. (2000). The labile brain. I. Neuronal transients and nonlinear coupling. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, 355, 215-36.
- Friston, K.J., Fletcher, P., Josephs, O., Holmes, A., Rugg, M.D., & Turner, R. (1998). Event-related fMRI, characterizing differential responses. *Neuroimage*, 7(1), 30-40.
- Frostig, R.D., Lieke, E.E., Ts'o, D.Y., & Grinvald, A. (1990). Cortical functional architecture and local coupling between neuronal activity and the microcirculation revealed by in vivo high-

- resolution optical imaging of intrinsic signals. *Proceedings of the National Academy of Sciences of the United States of America*, 87(16), 6082-6.
- Furlan, M., Marchal, G., Viader, F., Derlon, J.M., & Baron, J.C. (1996). Spontaneous neurological recovery after stroke and the fate of the ischemic penumbra. *Annals of Neurology*, 40(2), 216-226.
- Ghez, C. (1991). The Cerebellum. In Kandel, E.R., Schwartz, J.H., Jessel, T.M. (Eds.), *Principles of Neural Science*. Appleton and Lange, Connecticut.
- Grafton, S.T., Waters, C., Sutton, J., Lew, M.F., & Couldwell, W. (1995). Pallidotomy increases activity of motor association cortex in Parkinson's disease: a positron emission tomographic study. *Annals of Neurology*, 37(6), 776-783.
- Greene, L.S., & Williams, H.G. (1996). Aging and coordination from the dynamic pattern perspective. In: Fernandez, A.M., Teasdale, N. (Eds.) *Changes in sensory motor behavior in aging*. Amsterdam: Elsevier; 89-131.
- Gusnard, D.A. & Raichle, M.E. (2001). Searching for a baseline, Functional imaging and the resting human brain. *Nature reviews. Neuroscience*, 2 (10), 685-694.
- Guye, M., Parker, G.J., Symms, M., Boulby, P., Wheeler-Kingshott, C.A., Salek-Haddadi, A., Barker, G.J., & Duncan, J.S. (2003). Combined functional MRI and tractography to demonstrate the connectivity of the human primary motor cortex in vivo. *Neuroimage*, 19(4), 1349-60.
- Haken, H. (1996). *Principles of Brain Functioning, A Synergetic Approach to Brain Activity, Behavior and Cognition*, Springer Verlag.
- Hall, D.A., Haggard, M.P., Akeroyd, M.A., Palmer, A.R., Summerfield, A.Q., Elliott, M.R., Gurney, E.M., & Bowtell, R.W. (1999). "Sparse" temporal sampling in auditory fMRI. *Human Brain Mapping*, 7(3), 213-23.

- Hammeke, T.A. (2000). Functional MRI in Neurology. In Moonen, C.T.W. and Bandettini, P.A., (Eds.), *Functional MRI*, Springer Verlag.
- Harel, N., Lee, S.P., Nagaoka, T., Kim, D.S., & Kim, S-G. (2002). Origin of negative blood oxygenation level-dependent fMRI signals. *Journal of Cerebral Blood Flow and Metabolism*, 22(8), 908-17.
- Harrington, D.L., & Haaland, K.Y. (1999). Neural underpinnings of temporal processing: a review of focal lesion, pharmacological, and functional imaging research. *Reviews in the Neurosciences*, 10(2), 91-116.
- Harrington, D.L., Haaland, K.Y., & Hermanowicz, N. (1998). Temporal processing in the basal ganglia. *Neuropsychology*, 12(1), 3-12.
- Harrison, R.V., Harel, N., Panesar, J., & Mount, R.J. (2000). Blood capillary distribution correlates with hemodynamic-based functional imaging in the cerebral cortex. *Cerebral Cortex*, 3, 225-233.
- Haslinger, B., Erhard, P., Kampfe, N., Boecker, H., Rummeny, E., Schwaiger, M., Conrad, B., & Ceballos-Baumann, A.O. (2001). Event-related functional magnetic resonance imaging in Parkinson's disease before and after levodopa. *Brain*, 124(Pt 3), 558-570.
- Heeger, D.J., & Ress, D. (2002). What does fMRI tell us about neuronal activity? *Nature reviews. Neuroscience*, 3(2), 142-51.
- Heeger, D.J., Boynton, G.M., Demb, J.B., Seidemann, E., & Newsome, W.T. (1999). Motion opponency in visual cortex. *Journal of Neuroscience*, 19(16), 7162-74.
- Heeger, D.J., Huk, A.C., Geisler, W.S., & Albrecht, D.G. (2000). Spikes versus BOLD, what does neuroimaging tell us about neuronal activity? *Nature Neuroscience*, 3(7), 631-3.
- Heller, A., Wade, D.T., Wood, V.A., Sunderland, A., Langton-Hewer, R., & Wade, E. (1987). Arm function after stroke: Measurement and function over the first three months. *Journal of Neurology Neurosurgery and Psychiatry*, 50, 714-719.

- Hess, G., & Donoghue, J.P. (1996). Long-term depression of horizontal connections in rat motor cortex. *European Journal of Neuroscience*, 8(4), 658-665.
- Hoehn, M.M., & Yahr, M.C. (1967). Parkinsonism: onset, progression and mortality. *Neurology*, 17, 427-442.
- Horgan, N.F., & Finn, A.M. (1997). Motor recovery following stroke: a basis for evaluation. *Disability and rehabilitation*, 19(2); 64-70.
- Hornak, J., Rolls, E.T., & Wade, D. (1996). Face and voice expression identification in patients with emotional and behavioral changes following ventral frontal lobe damage. *Neuropsychologia*. 34(4), 247-61.
- Hu, X., Le, T.H., & Ugurbil, K. (1997). Evaluation of the early response in fMRI in individual subjects using short stimulus duration. *Magnetic Resonance in Medicine*, 37(6), 877-84.
- Hu, X., Yacoub, E., Le, T.H., & Cohen, E.R., & Ugurbil, K. (2000). Functional MRI signal decrease at the on set of stimulation. In Moonen, C.T.W. and Bandettini, P.A., (Eds.), *Functional MRI*, Springer Verlag.
- Hutchinson, S., Lee, L.H., Gaab, N., & Schlaug, G. (2003). Cerebellar volume of musicians. *Cerebral Cortex*, 13(9), 943-9.
- Hyder, F., Chase, J.R., Behar, K.L., Mason, G.F., Siddeek, M., Rothman, D.L., & Shulman, R.G. (1996). Increased tricarboxylic acid cycle flux in rat brain during forepaw stimulation detected with $^1\text{H}[^{13}\text{C}]$ NMR. *Proceedings of the National Academy of Sciences of the United States of America*, 93(15), 7612-7.
- Ito, M. Neurophysiological aspects of the cerebellar motor control system. *International Journal of Neurology*, 7, 162-176.
- Ivry, R. (1997). Cerebellar timing systems. *International review of neurobiology*, 41, 555-573.

- Ivry, R. and Keele, S. (1989). Timing functions of the cerebellum. *Journal of Cognitive Neuroscience*, 1, 136-152.
- Ivry, R.B., & Richardson, T.C. (2000). Temporal control and coordination: the multiple timer model. *Brain and Cognition*, 48(1), 117-132.
- Ivry, R.B., Keele, S.W., & Diener, H.C. (1988). Dissociation of the lateral and medial cerebellum in movement timing and movement execution. *Experimental Brain Research*, 73(1), 167-180.
- Jacobs, K.M., & Donoghue, J.P. (1991). Reshaping the cortical motor map by unmasking latent intracortical connections. *Science*, 251, 944-947.
- Janata, P., Birk, J.L., Van Horn, J.D., Leman, M., Tillmann, B., & Bharucha, J.J. (2002). The cortical topography of tonal structures underlying Western music. *Science*, 298(5601), 2167-70
- Jäncke, L. Himmelbach, M., Shah, N.J., & Zilles. K. (2000). The effect of switching between sequential and repetitive movements on cortical activation. *Neuroimage*, 12, 528-537.
- Jäncke, L., Kleinschmidt, A., Mirzazade, S., & Freund, H-J. (2001). The Sensorimotor Role of Parietal Cortex In Linking the Tactile Perception and Manual Construction of Object Shapes: An fMRI study. *Cerebral Cortex*, 11, 114-121.
- Jancke, L., Loose, R., Lutz, K., Specht, K., & Shah, N.J. (2000). Cortical activations during paced finger-tapping applying visual and auditory pacing stimuli. *Brain Research Cognitive Brain Research*, 10(1-2), 51-66.
- Jäncke, L., Peters, M., Schlaug, G., Posse, S., Steinmetz, H., & Muller-Gartner, H.W. (1998). Differential magnetic resonance signal change in human sensorimotor cortex to finger movements of different rate of the dominant and the subdominant hand. *Brain Research Cognitive Brain Research*, 6, 279-284.

- Jäncke, L., Specht, K., Mirzazade, S., & Peters, M. (1999). The effect of finger movement speed of the dominant and the subdominant hand on cerebellar activation: A functional Magnetic resonance imaging study. *Neuroimage*, 9, 497-507.
- Jantzen, K.J., Fuchs, A., Mayville, J.M., Deecke, L., & Kelso, J.A.S. (2001). Neuromagnetic activity in alpha and beta bands reflect learning-induced increases in coordinative stability. *Clinical Neurophysiology*, 112(9), 1685-97.
- Jantzen, K.J., Steinberg, F.L., & Kelso, J.A.S. (2002a). Practice-dependent modulation of neural activity during human sensorimotor coordination: a functional Magnetic Resonance Imaging study. *Neuroscience Letters*, 332(3), 205-209.
- Jantzen, K.J., Steinberg, F.L. & Kelso, J.A.S. (2002b). Neural mechanisms of timing depend on situational context. *Society for Neuroscience Abstract*, program no. 459.6.
- Jantzen, K.J., Steinberg, F.L., & Kelso, J.A.S. (2004). Brain networks underlying timing are influenced by prior context. Submitted to *Proceedings of the National Academy of Sciences of the United States of America*.
- Jeannerod, M. & Decety, J. (1995). Mental motor imagery: a window into the representational stages of action. *Current Opinions in Neurobiology*, 5, 727-732.
- Jeannerod, M. (1994). The representing brain: Neural correlates of motor intention and imagery. *The Behavioral and Brain Sciences*, 17, 187-245.
- Jenkins, W.M., Merzenich, M.M., Ochs, M.T., Allard, T., & Guis-Robles, E. (1990). Functional reorganization of primary somatosensory cortex in adult owl monkeys after behaviorally controlled tactile stimulation. *Journal of Neurophysiology*, 63, 82-104.
- Jirsa, V.K. & Kelso, J.A.S. (2000). Spatiotemporal pattern formation in neural systems with heterogeneous connection topologies. *Physical Review E*, 62, 8462-65.

- Jirsa, V.K., Jantzen, K.J., Fuchs, A & Kelso, J.A.S. (2001). Neural field dynamics on the folded three-dimensional cortical sheet and its forward EEG and MEG. In: M.F Insana, R.M. Leahy (Eds), *IPMI 2001*, LNCS 2082, Springer-Verlag Berlin Heidelberg, 286–299.
- Johnson, K.A., Cunnington, R., Bradshaw, J.L., Phillips, J.G., Iansek, R., & Rogers, M.A. (1998). Bimanual co-ordination in Parkinson's disease. *Brain*, 121 (Pt 4), 743-753.
- Johnson, S.H. (2000). Imagining the impossible: intact motor representations in hemiplegics. *Neuroreport*, 11(4), 729-732.
- Jones, M., Berwick, J., Johnston, D., & Mayhew, J. (2001). Concurrent optical imaging spectroscopy and laser-Doppler flowmetry, the relationship between blood flow, oxygenation, and volume in rodent barrel cortex. *Neuroimage*, 13(6 Pt 1), 1002-15.
- Jones, T.A., & Schallert, T. (1992). Overgrowth and pruning of dendrites in adult rats recovering from neocortical damage. *Brain Research*, 581, 156-160.
- Jones, T.A., & Schallert, T. (1994). Use-dependent growth of pyramidal neurons after neocortical damage. *Journal of Neuroscience*, 14, 2140-2152.
- Jones, T.A., Kleim, J.A., & Greenough, W.T. (1996). Synaptogenesis and dendritic growth in the cortex opposite unilateral sensorimotor cortex damage in adult rats: a quantitative electron microscopic examination. *Brain Research*, 733, 142-148.
- Jueptner, M., Rijntjes, M., Weiller, C., Faiss, J.H., Timmann, D., Mueller, S.P., & Diener, H.C. (1995). Localization of a cerebellar timing process using PET. *Neurology*, 45(8), 1540-1545.
- Juslin, P.N. (2001). Communicating emotion in music performance: A review and theoretical framework. In *Music and Emotion: Theory and Practice*. Sloboda, J.A., Juslin, P.N. (Eds.) Oxford University Press Increase, New York.
- Kaasinen, V., & Rinne, J.O. (2002). Functional imaging studies of dopamine system and cognition in normal aging and Parkinson's disease. *Neuroscience and biobehavioral reviews*, 26(7), 785-793.

- Karni, A. (1996). The acquisition of perceptual and motor skills: a memory system in the adult human cortex *Brain Research Cognitive Brain Research*, 5(1-2), 39-48.
- Karni, A., Meyer, G., Jezzard, P., Adams, M.M., Turner, R., & Ungerleider, L.G. (1995). Functional MRI evidence for adult motor cortex plasticity during motor skill learning. *Nature*, 377(6545), 155-158.
- Kawashima, R., Okuda, J., Umetsu, A., Sugiura, M., Inoue, K., Suzuki, K., Tabuchi, M., Tsukiura, T., Narayan, S.L., Nagasaka, T., Yanagawa, I., Fujii, T., Takahashi, S., Fukuda, H., & Yamadori, A. (2000). Human cerebellum plays an important role in memory-timed finger movement: an fMRI study. *Journal of Neurophysiology*, 83(2), 1079-1087.
- Keenan, J.P., Thangaraj, V., Halpern, A.R., & Schlaug, G. (2001). Absolute pitch and planum temporale. *Neuroimage*, 14(6), 1402-8.
- Kelso, J. A. S. & Zanone, P-G. (2002). Coordination Dynamics of learning and transfer across different effector systems. *Journal of Experimental Psychology: Human Perception and Performance*, 28(4), 776-97.
- Kelso, J.A.S. & Stelmach, G.E. (1976). Central and peripheral mechanisms in motor control, In G.E. Stelmach (Ed.), *Motor control: Issues and Trends*. New York, London, Academic Press, 1-40.
- Kelso, J.A.S. (1995). *Dynamic Patterns: The Self-Organization of Brain and Behavior*. Cambridge: MIT Press.
- Kelso, J.A.S., Bressler, S.L., Buchanan, S., DeGuzman, G.C., Ding, M., Fuchs, A. & Holroyd, T. (1992). A phase transition in human brain and behavior. *Physics Letters A*, 169, 134-144.
- Kelso, J.A.S., DelColle, J. & Schöner, G. (1990). Action-Perception as a pattern formation process. In M. Jeanerod (Ed.), *Attention and Performance XIII*, Hillsdale, NJ: Erlbaum, 139-169.

- Kelso, J.A.S., Fink, P., DeLaplain, C., & Carson, R.G. (2001). Haptic information stabilizes and destabilizes coordination dynamics, *Proceedings of the Royal Society of London. Series B. Biological sciences*, 268, 1207-1213.
- Kim, D.S., Duong, T.Q., & Kim, S-G. (2000a). High-resolution mapping of iso-orientation columns by fMRI. *Nature Neuroscience*, 3(2), 164-9.
- Kim, S-G, & Duong, T.Q. (2002). Mapping cortical columnar structures using fMRI. *Physiology and Behavior*, 77(4-5), 641-4.
- Kim, S-G., Ashe, J., Hendrich, K., Ellermann, J.M., Merkle, H., Ugurbil, K., & Georgopoulos, A.P. (1993). Functional magnetic resonance imaging of the motor cortex: hemispheric asymmetry and handedness. *Science*, 261, 615-617.
- Kim, S-G., Hendrich, K., Hu, X., Merkle, H., & Ugurbil, K. (1994). Potential pitfalls of functional MRI using conventional gradient-recalled echo techniques. *NMR in Biomedicine*, 7(1-2), 69-74.
- Kim, S-G., Lee, S.P., Goodyear, B., & Dilva, A.C. (2000b). Spatial resolution of BOLD and other fMRI techniques. In Moonen, C.T.W. and Bandettini, P.A., (Eds.), *Functional MRI*, Springer Verlag.
- Koski, L., & Paus, T. (2000). Functional connectivity of the anterior cingulate cortex within the human frontal lobe: a brain-mapping meta-analysis. *Experimental Brain Research*, 133(1), 55-65.
- Kosslyn, S.M. (1999). If neuroimaging is the answer, what is the question? *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, 354(1387), 1283-94.
- Kosslyn, S.M., Ganis, G., & Thompson, W.L. (2001). Neural foundations of imagery. *Nature Reviews Neuroscience*, 2(9), 635-42.

- Kozlowski, D.A., James, D.C., & Schallert, T. (1996). Use-dependent exaggeration of neuronal injury after unilateral sensorimotor cortex lesions. *Journal of Neuroscience*, 16, 4776-4786.
- Kraut, R. (1992). On the possibility of a determinate semantics for music, In Jones, M. R. & Holleran, S. (Eds.) *Cognitive Bases of Musical Communication*, Washington, DC, APA.
- Krumhansl, C.L. (1997). An exploratory study of musical emotions and psychophysiology, *Canadian Journal of Experimental Psychology*, 51(4), 336-352.
- Kurthen, M., Reichmann, K., Linke, D.B., Biersack, H.J., Reuter, B.M., Durwen, H.F., & Grunwald, F. (1990). Crossed cerebellar diaschisis in intracarotid sodium amytal procedures: a SPECT study. *Acta Neurologica Scandinavica*, 81(5), 416-422.
- Kuschinsky, W. (2000). Regulation of cerebral blood flow. In Moonen, C.T.W. and Bandettini, P.A., (Eds.), *Functional MRI*, Springer Verlag.
- Lai, S., Hopkins, A.L., Haacke, E.M., Li, D., Wasserman, B.A., Buckley, P., Friedman, L., Meltzer, H., Hedera, P., & Friedland, R. (1993). Identification of vascular structures as a major source of signal contrast in high resolution 2D and 3D functional activation imaging of the motor cortex at 1.5T, preliminary results. *Magnetic Resonance in Medicine*, 30(3), 387-92.
- Lancaster, J.L., Fox, P.T., Mikiten, S. & Rainey, L. (1997). The Talairach daemon, Available from URL, <http://biad73.uthscsa.edu/>
- Lange, K.W., Paul, G.M., Naumann, M., & Gsell, W. (1995). Dopaminergic effects on cognitive performance in patients with Parkinson's disease. *Journal of neural transmission. Supplementum*, 46, 423-432.
- Langer, S. (1951). *Philosophy in a new key*. (2nd Edition). New York: New American Library.
- Large, E.W., & Jones, M. R. (1999). The dynamics of attending: How we track time-varying events, *Psychological Review*, 106 (1), 119-159.

- Large, E.W., & Palmer, C. (2002). Perceiving temporal regularity in music, *Cognitive Science*, 26, 1-37.
- Lee, A.T., Glover, G.H., & Meyer, C.H. (1995). Discrimination of large venous vessels in time-course spiral blood-oxygen-level-dependent magnetic-resonance functional neuroimaging. *Magnetic Resonance in Medicine*, 33(6), 745-54.
- Lee, D.J., Chen, Y., & Schlaug, G. (2003), Corpus callosum: musician and gender effects. *Neuroreport*, 14(2), 205-9.
- Lejeune, H., Maquet, P., Bonnet, M., Casini, L., Ferrara, A., Macar, F., Pouthas, V., Timsit-Berthier, M., & Vidal, F. (1997). The basic pattern of activation in motor and sensory temporal tasks: positron emission tomography data. *Neuroscience Letters*, 235(1-2), 21-24.
- Levitin, D.J., & Menon, V. (2003). Musical structure is processed in "language" areas of the brain: a possible role for Brodmann Area 47 in temporal coherence. *Neuroimage*, 20(4), 2142-52.
- Levy, C.E., Nichols, D.S., Schmalbrock, P.M., Keller, P., & Chakeres, D.W. (2001). Functional MRI evidence of cortical reorganization in upper-limb stroke hemiplegia treated with constraint-induced movement therapy. *American Journal of Physical Medicine and Rehabilitation*, 80, 4-12.
- Lewis, P., & Miall, C. (2003). In: *Functional and Neural Mechanisms of Interval Timing*, ed. Meck, W. CRC Press, Boca Raton, 515-532.
- Li, Y., Jiang, N., Powers, C., & Chopp, M. (1998). Neuronal damage and plasticity identified by microtubule-associated protein 2, growth-associated protein 43, and cyclin D1 immunoreactivity after focal cerebral ischemia in rats. *Stroke*, 29(9), 1972-1980; discussion 1980-1981.
- Liegeois-Chauvel, C., Peretz, I., Babai, M., Laguitton, V. & Chauvel, P. (1998). Contribution of different cortical areas in the temporal lobe to music processing, *Brain*, 121, 1853-1867.

- Liepert, J., Terborg, C., & Weiller, C. (1999). Motor plasticity induced by synchronized thumb and foot movements. *Experimental Brain Research*, 125, 435-439.
- Lin, W.Y., Kao, C.H., Wang, P.Y., Changlai, S.P., & Wang, S.J. (1996). Serial changes in regional blood flow in the cerebrum and cerebellum of stroke patients imaged by $^{99}\text{Tc}^{\text{m}}$ -HMPAO SPET. *Nuclear Medicine Communications*, 17, 208-211.
- Lindauer, U., Rojl, G., Leithner, C., Kuhl, M., Gold, L., Gethmann, J., Kohl-Bareis, M., Villringer, A., & Dirnagl, U. (2001). No evidence for early decrease in blood oxygenation in rat whisker cortex in response to functional activation. *Neuroimage*, 13(6 Pt 1), 988-1001.
- Logothetis, N.K., Pauls, J., Augath, M., Trinath, T., & Oeltermann, A. (2001). Neurophysiological investigation of the basis of the fMRI signal. *Nature*, 412(6843), 150-7.
- Lotze, M., Montoya, P., Erb, M., Hulsmann, E., Flor, H., Klose, U., Birbaumer, N., & Grodd, W. (1999). Activation of cortical and cerebellar motor areas during executed and imagined hand movements: An fMRI study. *Journal of Cognitive Neuroscience*, 11, 491-501.
- Lotze, M., Scheler, G., Tan, H.R., Braun, C., & Birbaumer, N. (2003). The musician's brain: functional imaging of amateurs and professionals during performance and imagery. *Neuroimage*, 20(3), 1817-29.
- Luft, A.R., Skalej, M., Stefanou, A., Klose, U., & Voigt, K. (1989). Comparing Motion and Imagery related activation in the human cerebellum: A functional MRI study. *Human Brain Mapping*, 6, 105-113.
- MacDonald, A.W., Cohen, J.D., Stegner, V.A., & Carter, C.S. (2000). Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science*, 288, 1835-38.
- Maddock, R.J. (1999). The retrosplenial cortex and emotion: new insights from functional neuroimaging of the human brain. *Trends in Neurosciences*, 22(7), 310-6.

- Maddock, R.J., Garrett, A.S., & Buonocore, M.H. (2003). Posterior cingulate cortex activation by emotional words: fMRI evidence from a valence decision task. *Human Brain Mapping*, 18(1), 30-41.
- Magistretti, P.J., & Pellerin, L. (1999). Cellular mechanisms of brain energy metabolism and their relevance to functional brain imaging. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, 354(1387), 1155-63.
- Magistretti, P.J., & Pellerin, L. (2000). Regulation of cerebral energy metabolism. In Moonen, C.T.W. and Bandettini, P.A., (Eds.), *Functional MRI*, Springer Verlag.
- Malapani, C., Rakitin, B., Levy, R., Meck, W.H., Deweer, B., Dubois, B., & Gibbon, J. (1998). Coupled temporal memories in Parkinson's disease: a dopamine-related dysfunction. *Journal of Cognitive Neuroscience*, 10(3), 316-331.
- Malonek, D., & Grinvald, A. (1996). Interactions between electrical activity and cortical microcirculation revealed by imaging spectroscopy, implications for functional brain mapping. *Science*, 272(5261), 551-4.
- Mangels, J.A., Ivry, R.B., & Shimizu, N. (1998). Dissociable contributions of the prefrontal and neocerebellar cortex to time perception. *Brain Research Cognitive Brain Research*, 7(1), 15-39.
- Maquet, P., Lejeune, H., Pouthas, V., Bonnet, M., Casini, L., Macar, F., Timsit-Berthier, M., Vidal, F., Ferrara, A., Degueldre, C., Quaglia, L., Delfiore, G., Luxen, A., Woods, R., Mazziotta JC, Comar D. (1996). Brain activation induced by estimation of duration: a PET study. *Neuroimage*, 3(2), 119-26.
- Marshall, R.S., Perera, G.M., Lazar, R.M., Krakauer, J.W., Constantine, R.C., & DeLaPaz, R.L. (2000). Evolution of cortical activation during recovery from corticospinal tract infarction. *Stroke*, 31, 656-661.

- Mattay, V.S., Tessitore, A., Callicott, J.H., Bertolino, A., Goldberg, T.E., Chase, T.N., Hyde, T.M., & Weinberger, D.R. (2002). Dopaminergic modulation of cortical function in patients with Parkinson's disease. *Annals of Neurology*, 51(2), 156-64.
- Mayville, J.M., Jantzen, K.J., Fuchs, A., Steinberg, F.L., & Kelso, J.A.S. (2002). Cortical and subcortical networks underlying syncopated and synchronized coordination revealed using fMRI. *Human Brain Mapping*, 17, 214-229.
- Mazziotta, J.C., & Comar, D. (1996). Brain activation induced by estimation of duration: a PET study. *Neuroimage*, 3(2), 119-126.
- McCarthy, G., Luby, M., Gore, J., & Goldman-Rakic, P. (1997). Infrequent events transiently activate human prefrontal and parietal cortex as measured by functional MRI. *Journal of Neurophysiology*, 77(3), 1630-4.
- McIntosh, G.C., Brown, S.H., Rice, R.R., & Thaut, M.H. (1997). Rhythmic auditory-motor facilitation of gait patterns in patients with Parkinson's disease, *Journal of Neurology Neurosurgery and Psychiatry*, 62, 22-26.
- McKiernan, K.A., Kaufman, J.N., Thompson, J.K., & Binder, J.R. (2003). A parametric manipulation of factors affecting task-induced deactivation in functional neuroimaging. *Journal of Cognitive Neuroscience*, 15(3), 394-408.
- Meck, W.H. (1996). Neuropharmacology of timing and time perception. *Cognitive Brain Research*, 3, 227-242.
- Menon, R.S., & Goodyear, B.G. (1999). Submillimeter functional localization in human striate cortex using BOLD contrast at 4 Tesla, implications for the vascular point-spread function. *Magnetic Resonance in Medicine*, 41(2), 230-5.
- Menon, R.S., & Kim, S-G. (1999). Spatial and temporal limits in cognitive neuroimaging with fMRI. *Trends in Cognitive Sciences*, 3 (6), 207-216.

- Menon, R.S., Ogawa, S., Hu, X., Strupp, J.P., Anderson, P., & Ugurbil, K. (1995). BOLD based functional MRI at 4 Tesla includes a capillary bed contribution, echo-planar imaging correlates with previous optical imaging using intrinsic signals. *Magnetic Resonance in Medicine*, 33(3), 453-9.
- Menon, R.S., Ogawa, S., Strupp, J.P., & Ugurbil, K. (1997). Ocular dominance in human V1 demonstrated by functional magnetic resonance imaging. *Journal of Neurophysiology*, 77(5), 2780-7.
- Menon, R.S., Ogawa, S., Tank, D.W., & Ugurbil, K. (1993). 4Tesla gradient recalled echo characteristics of photic stimulation-induced signal changes in the human primary visual cortex. *Magnetic Resonance in Medicine*, 30(3), 380-6.
- Merzenich, M.M., Nelson, R.J., Stryker, M.P., Cynader, M.S., Schoppmann, A., & Zook, J.M. (1984). Somatosensory cortical map changes following digit amputation in adult monkeys. *The journal of comparative Neurology*, 224, 591-605.
- Mesulam, M-M. (1985). Patterns in behavioral neuroanatomy: Association areas, the limbic system and hemispheric specialization. In *Principles of Behavioral Neurology* (M-M. Mesulam Ed.), F.A.Davis Co., Philadelphia, 1-70.
- Mewasingh, L.D., Christiaens, F., Aeby, A., Christophe, C., & Dan, B. (2002). Crossed cerebellar diaschisis secondary to refractory frontal seizures in childhood. *Seizure*, 11(8), 489-493.
- Meyer, L.B. (1956). *Emotion and meaning in music*, Chicago: University of Chicago Press.
- Meyer-Lindenberg, A., Ziemann, U., Hajak, G., Cohen, L., & Berman, K.F. (2002). Transitions between dynamical states of differing stability in the human brain. *Proceedings of the National Academy of Sciences of the United States of America*, 99, 10948-10953.
- Middleton, F.A., & Strick, P.L. (1997a). New concepts about the organization of basal ganglia output. *Advances in Neurology*, 74, 57-68.

- Middleton, F.A., & Strick, P.L. (1997b). Cerebellar output channels. *International review of neurobiology*, 41, 61-82.
- Miller, E.K., & Cohen, J.D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience*, 24, 167-202.
- Miura, H., Nagata, K., Hirata, Y., Satoh, Y., Watahiki, Y., & Hatazawa, J. (1994). Evolution of crossed cerebellar diaschisis in middle cerebral artery infarction. *Journal of Neuroimaging*, 4(2), 91-96.
- Monno, A., Temprado, J.J., Zanone, P.G., & Laurent, M. (2002). The interplay of attention and bimanual coordination dynamics. *Acta psychologica*, 110(2-3), 187-211.
- Morgello, S., Uson, R.R., Schwartz, E.J., & Haber, R.S. (1995). The human blood-brain barrier glucose transporter (GLUT1) is a glucose transporter of gray matter astrocytes. *Glia*, 14, 43-54.
- Nair, D.G., Large, E.W., Steinberg, F.L., & Kelso, J.A.S. (2002). Perceiving emotion in expressive piano performance: A functional MRI study. *Proceedings of the 7th International Conference on Music Perception and Cognition*, Sydney; C.Stevens, D.Burnham, E. Schubert, J.Renwich (Eds). Adelaide: Causal Productions; 627-630.
- Nair, D.G., Purcott, K.L., Fuchs, A., Steinberg, F.L., & Kelso, J.A.S. (2003). Cortical and cerebellar activity of the human brain during imagined and executed unimanual and bimanual action sequences: A functional MRI study. *Cognitive Brain Research*, 15(3), 250-260.
- Neale, J.M., & Liebert, R.M. (1986). *Science and behavior*. Englewood Cliffs, NJ: Prentice Hall.
- Nelles, G., Spiekermann, G., Jueptner, M., Leonhart G., Müller, S., Gerhard, H., & Diener, C.H. (1999). Evolution of functional reorganization in hemiplegic stroke: A serial Positron Emission Tomographic activation study. *Annals of Neurology*, 46, 901-909.

- Nenadic, I., Gaser, C., Volz, H.P., Rammsayer, T., Hager, F., & Sauer, H. (2003). Processing of temporal information and the basal ganglia: new evidence from fMRI. *Experimental Brain Research*, 148(2), 238-246.
- Netz, J., Lammers, T., & Homberg, V. (1997). Reorganization of motor output in the non-affected hemisphere after stroke. *Brain*, 120 (Pt 9), 1579-1586.
- Nudo, R.J. (1999). Recovery after damage to motor cortical areas. *Current Opinion in Neurobiology*, 9, 740-747.
- Nudo, R.J., Plautz, E.J., & Frost, S.B. (2001). Role of adaptive plasticity in recovery of function after damage to motor cortex. *Muscle Nerve*, 24, 1000-1019.
- Nudo, R.J., Wise, B.M., SiFuentes, F., & Milliken, G.W. (1996). Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct. *Science*, 272, 1791-1794.
- Nuutinen, J., Kuikka, J., Roivainen, R., Vanninen, E., & Sivenius, J. (2000). Early serial SPET in acute middle cerebral artery infarction. *Nuclear Medicine Communications*, 21, 425-429.
- O'Boyle, D.J., Freeman, J.S., & Cody, F.W. (1996). The accuracy and precision of timing of self-paced, repetitive movements in subjects with Parkinson's disease. *Brain*, 119(Pt1), 51-70.
- Ogawa, S., Lee, T.M., Kay, A.R., & Tank, D.W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences of the United States of America*, 87, 9868-9872.
- Ohnishi, T., Matsuda, H., Asada, T., Aruga, M., Hirakata, M., Nishikawa, M., Katoh, A., & Imabayashi, E. (2001). Functional anatomy of musical perception in musicians. *Cerebral Cortex*, 11(8), 754-60.
- Oscarsson, O. (1965). Functional organization of the spino- and cuneocerebellar tracts. *Physiological Reviews*, 45, 495-522.

- Oschner, K.N., Bunge, S.A., Gross, J.J., & Gabrieli, J.D.E. (2002). Rethinking feelings: An fMRI study of the cognitive regulation of emotion. *Journal of Cognitive Neuroscience*, 14,8, 1215-1229.
- Otte, A., Roelcke, U., von Ammon, K., Hausmann, O., Maguire, R.P., Missimer, J., Muller-Brand, J., Radu, E.W., & Leenders, K.L. (1998). Crossed cerebellar diaschisis and brain tumor biochemistry studied with positron emission tomography, [18F]fluorodeoxyglucose and [11C]methionine. *Journal of the Neurological Sciences*, 156(1), 73-77.
- Palmer, C. (1997). Music performance, *Annual review of psychology*, 48, 115-138.
- Pandya, D.N., & Yeterian, E.H. (1985). Architecture and connections of cortical association areas. In: Peters, A., Jones, E.G., editors. *Cerebral Cortex*, Vol. 4. New York: Plenum Press, 3-61.
- Pastor, M.A., Jahanshahi, M., Artieda, J., & Obeso, J.A. (1992). Performance of repetitive wrist movements in Parkinson's disease. *Brain*, 115(Pt 3), 875-91.
- Patel, A., Peretz, I., Tramo, M., & Labrecque, R. (1998). Processing prosodic and musical patterns: A neuropsychological investigation, *Brain and Language*, 61, 123-144.
- Patel, A.D. (2003). Language, music, syntax and the brain. *Nature Neuroscience*, 6(7), 674-81.
- Pellerin, L., & Magistretti, P.J. (1994). Glutamate uptake in astrocytes stimulates aerobic glycolysis, a mechanism coupling neuronal activity to glucose utilization. *Proceedings of the National Academy of Sciences of the United States of America*, 91, 10625-29.
- Penhune, V. B., Zatorre, R.J., & Evans, A.C. (1998). Cerebellar contributions to motor timing: A PET study of auditory and visual rhythm reproduction. *Journal of Cognitive Neuroscience*, 10, 752-765.
- Peretz, I., Gagnon, L. & Bouchard, B. (1998). Music and emotion: perceptual determinants, immediacy and isolation after brain damage, *Cognition*, 68, 111-141.

- Platel, H., Baron, J.C., Desgranges, B., Bernard, F., & Eustache, F. (2003). Semantic and episodic memory of music are subserved by distinct neural networks. *Neuroimage*, 20(1), 244-56.
- Platel, H., Price, C., Baron, J.C., Wise, R., Lambert, J., Frackowiak, R.S., Lechevalier, B., & Eustache, F. (1997). The structural components of music perception. A functional anatomical study. *Brain*, 120 (Pt 2), 229-43.
- Playford, E.D., Jenkins, I.H., Passingham, R.E., Nutt, J., Frackowiak, R.S., & Brooks, D.J. (1992). Impaired mesial frontal and putamen activation in Parkinson's disease: a positron emission tomography study. *Annals of Neurology*, 32(2), 151-161.
- Porro, C.A., Francescato, M.P., Cettolo, V., Diamond, M.E., Baraldi, P., Zuiani, C., Bazzocchi, M., & Prampero, P.E. (1996). Primary motor and sensory cortex activation during motor performance and motor imagery: a functional Magnetic Resonance Imaging study. *Journal of Neuroscience*, 16, 7688-7698.
- Prichard, D., Rothman, E., Novotny, E., Petroff, T., Kuwabara, M., Avison, A., Howseman, C., & Hanstock, S.R. (1991). Lactate rise detected by ¹H NMR in human visual cortex during physiologic stimulation. *Medical Science*, 88, 5829-31.
- Qu, M., Buchkremer-Ratzmann, I., Schiene, K., Schroeter, M., Witte, O.W., & Zilles, K. (1998). Bihemispheric reduction of GABA-A receptor binding following focal cortical photothrombotic lesions in the rat brain. *Brain Research*, 813(2), 374-380.
- Raffman, D. (1992). Proposal for a musical semantics. In Jones, M. R. & Holleran, S. (Eds.) *Cognitive Bases of Musical Communication*, Washington, DC, APA
- Raichle, M.E. (1998). Behind the scenes of functional brain imaging, a historical and physiological perspective. *Proceedings of the National Academy of Sciences of the United States of America*, 95(3), 765-72.

- Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., & Gusnard, D.A. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America*, 98(2), 676-682.
- Rammsayer, T. (1989). Is there a common dopaminergic basis of time perception and reaction time? *Neuropsychobiology*, 21(1), 37-42.
- Rammsayer, T.H. (1993). On dopaminergic modulation of temporal information processing. *Biological Psychology*, 36, 209-222.
- Rammsayer, T.H. (1999). Neuropharmacological evidence for different timing mechanisms in humans. *The Quarterly journal of experimental psychology. B, Comparative and physiological psychology*, 52, 273-286.
- Rammsayer, T.H., & Lima, S.D. (1991). Duration discrimination of filled and empty auditory intervals - Cognitive and perceptual factors. *Perception and Psychophysics*, 50, 565-574.
- Rao, S.M., Bandettini, P.A., Binder, J.R., Bobholz, J.A., Hameke, T.A., Stein, E.A., & Hyde, J.S. (1996). Relationship between finger movement rate and functional magnetic resonance signal change in human primary motor cortex. *Journal of Cerebral Blood Flow and Metabolism*, 16, 1250-1254.
- Rao, S.M., Binder, J.R., Bandettini, P.A., Hammekke, T.A., Yetkin, F.Z., Jesmanowicz, A., Lisk, L.M., Morris, G.L., Muller, W.M., Estkowski, L.D., Wong, E.C., Haughton, E.M., & Hyde, J.S. (1993). Functional magnetic resonance imaging of complex human movements. *Neurology*, 43, 2311-2318.
- Rao, S.M., Harrington, D.L., Haaland, K.Y., Bobholz, J.A., Cox, R.W., & Binder, J.R. (1997). Distributed neural systems underlying the timing of movements. *Journal of Neuroscience*, 17: 5528-5535.
- Rao, S.M., Mayer, A.R., & Harrington, D.L. (2001). The evolution of brain activation during temporal processing. *Nature Neuroscience*, 4, 317-323.

- Rascol, O., Sabatini, U., Fabre, N., Brefel, C., Loubinoux, I., Celsis, P., Senard, J.M., Montastruc, J.L., & Chollet, F. (1997). The ipsilateral cerebellar hemisphere is overactive during hand movements in akinetic parkinsonian patients. *Brain*, 120 (Pt 1), 103-110.
- Rees, G., Friston, K., & Koch, C. (2000). A direct quantitative relationship between the functional properties of human and macaque V5. *Nature Neuroscience*, 3(7), 716-23.
- Repp, B.H. (1998a). Variations on a theme by Chopin: Relations between perception and production of deviations from isochrony in music. *Journal of Experimental Psychology: Human Perception and Performance*, 24, 791-811.
- Repp, B.H. (1998b). A microcosm of musical expression: I. Quantitative analysis of pianists' timing in the initial measures of Chopin's Etude in E major. *Journal of the Acoustical Society of America*, 104, 1085-1100.
- Repp, B.H. (1999a). A microcosm of musical expression: II. Quantitative analysis of pianists' dynamics in the initial measures of Chopin's Etude in E major. *Journal of the Acoustical Society of America*, 105(3), 1972-1988.
- Repp, B.H. (1999b). A microcosm of musical expression: III. Contributions of timing and dynamics to the aesthetic impression of pianists' performances of the initial measures of Chopin's Etude in E major. *Journal of the Acoustical Society of America*, 106, 469-478.
- Repp, B.H. (1999c). Relationships between performance timing, perception of timing perturbations, and perceptual-motor synchronization in two Chopin preludes. *Australian Journal of Psychology*, 51, 188-203.
- Repp, B.H. (1999d). Individual differences in the expressive shaping of a musical phrase: the opening of Chopin's Etude in E major. In Yi, S.W. (ed.), *Music, mind, and science* (pp. 239-270). Seoul, Korea: Seoul National University Press.

- Richter, W., Andersen, P.M., Georgopoulos, A.P., & Kim S-G. (1997a). Sequential activity in human motor areas during a delayed cued finger movement task studied by time-resolved fMRI. *Neuroreport*, 8(5), 1257-61.
- Richter, W., Ugurbil, K., Georgopoulos, A., & Kim, S-G. (1997b) Time-resolved fMRI of mental rotation. *Neuroreport*, 8(17), 3697-702.
- Rijntjes, M., & Weiller, C. (2002). Recovery of motor and language abilities after stroke: the contribution of functional imaging. *Progress in Neurobiology*, 66(2), 109-122.
- Rioul-Pedotti, M.S., Friedman, D., Hess, G., & Donoghue, J.P. (1998). Strengthening of horizontal cortical connections following skill learning. *Nature Neuroscience*, 1(3), 230-234.
- Robinson, M.D. & Dowd, L.A. (1997). Heterogeneity and functional properties of subtypes of sodium dependent glutamate transporters in the mammalian central nervous system. *Advances in Pharmacology*, 37, 69-115.
- Roland, P.E., Skinhoj, E., & Lassen, A. (1981). Focal activations of human cerebral cortex during auditory discrimination. *Journal of Neurophysiology*, 45, 1139-1151.
- Roth, M., Decety, J., Raybaudi, M., Massarelli, R., Delon-Martin, C., Segebarth, C., Morand, S., Gemignani, A., Decorps, M., & Jeannerod, M. (1996). Possible involvement of the primary motor cortex in the mentally simulated movement: a functional magnetic resonance study. *Neuroreport*, 7, 1280-1284.
- Röther, J., Knab, R., Hamzei, F., Fiehler, J., Reichenbach, J.R., Buchel, C., & Weiller, C. (2002). Negative dip in BOLD fMRI is caused by blood flow--oxygen consumption uncoupling in humans. *Neuroimage*, 15(1), 98-102.
- Sabatini, U., Boulanouar, K., Fabre, N., Martin, F., Carel, C., Colonnese, C., Bozzao, L., Berry, I., Montastruc, J.L., Chollet, F., & Rascol, O. (2000). Cortical motor reorganization in akinetic patients with Parkinson's disease: a functional MRI study. *Brain*, 123 (Pt 2), 394-403.

- Samuel, M., Ceballos-Baumann, A.O., Blin, J., Uema, T., Boecker, H., Passingham, R.E., & Brooks, D.J. (1997). Evidence for lateral premotor and parietal overactivity in Parkinson's disease during sequential and bimanual movements. A PET study. *Brain*, 120 (Pt 6), 963-976.
- Sanes, J.N., & Donoghue, J.P. (2000). Plasticity and primary motor cortex. *Annual Reviews of Neuroscience*, 23, 393-415.
- Sanes, J.N., Wang, J., & Donoghue, J.P. (1992). Immediate and delayed changes in rat motor cortical output representation with new forelimb configurations. *Cerebral Cortex*, 2, 141-152.
- Schacter, S., & Singer, J.E. (1962). Cognitive, social and physiological determinants of emotional state, *Psychological Review*, 69, 379-399.
- Schieber, M.H. (1995). Muscular production of individuated finger movements: The role of extrinsic finger muscles. *Journal of Neuroscience*, 15, 284-297.
- Schlaug, G. (2001). The brain of musicians. A model for functional and structural adaptation. *Annals of the New York Academy of Sciences*, 930, 281-99.
- Schmahmann, J.D., & Pandya, D.N. (1989). Anatomical investigation of projections to the basis pontis from posterior parietal association cortices in rhesus monkey. *The Journal of comparative neurology*, 289, 53-73.
- Schmahmann, J.D., & Pandya, D.N. (1990). Anatomical investigation of projections from thalamus to the posterior parietal association cortices in rhesus monkey. *The Journal of comparative neurology*, 295, 299-326.
- Schmithorst, V.J., & Holland, S.K. (2003). The effect of musical training on music processing: a functional magnetic resonance imaging study in humans. *Neuroscience Letters*, 348, 65-68.

- Schubert, T., von Cramon, D.Y., Niendorf, T., Pollmann, S., & Bublak, P. (1998). Cortical areas and the control of self-determined finger movements: an fMRI study. *Neuroreport*, 9, 3171-3176.
- Schubotz, R.I., Friederici, A.D., & von Cramon, D.Y. (2000). Time perception and motor timing: A common cortical and subcortical basis revealed by fMRI. *Neuroimage*, 11, 1-12.
- Schwab, R.S., & England, A.C. (1969). Unified Parkinson's disease rating scale [UPDRS] Schwab and England activities of daily living scale. In: Herndon RM (1997), *Handbook of Clinical Neurologic Scales*. New York: Demos Vermande. 81-91.
- Seitz, R.J., Hoflich, P., Binkofski, F., Tellmann, L., Herzog, H., & Freund H-J. (1998). Role of the premotor cortex in recovery from middle cerebral artery infarction. *Archives of Neurology*, 55, 1081-1088.
- Shibasaki, H., Sadato, N., Lyshkow, H., Yonekura, Y., Honda, M., Nagamine, T., Suwazono, S., Magata, Y., Ikeda, A., Miyazaki, M., Fukuyama, H., Asato, R., & Konishi, J. (1993). Both primary motor cortex and supplementary motor area play an important role in complex finger movement. *Brain*, 116, 1387-1398.
- Shulman, G.L., Fiez, J.A., Corbetta, M., Buckner, R.L., Miezin, F.M., Raichle, M.E., & Peterson, S.E. (1997). Common blood flow changes across visual tasks, II. Decreases in cerebral cortex. *Journal of Cognitive Neuroscience*, 9, 648-663.
- Singh, L.N., Higano, S., Takahashi, S., Kurihara, N., Furuta, S., Tamura, H., Shimanuki, Y., Mugikura, S., Fujii, T., Yamadori, A., Sakamoto, M., & Yamada, S. (1998). Comparison of ipsilateral activation between right and left handers: a functional MR imaging study. *Neuroreport*, 9, 1861-1866.
- Sloboda, J.A. (1991). Music structure and emotional response: some empirical findings, *Psychology of Music*, 19, 110-120.

- Sloboda, J.A., & Juslin, P.N. (2001), Psychological perspectives on music and emotion. In *Music and Emotion: Theory and Practice*. Sloboda, J.A., Juslin, P.N. (Eds.) Oxford University Press Increase, New York.
- Sokoloff, L. (1981). Localization of functional activity in the central nervous system by measurement of glucose utilization with radioactive deoxyglucose. *Journal of Cerebral Blood Flow Metabolism*, 1, 7-36.
- Sokoloff, L. (1989). Circulation and energy metabolism of the brain. In Siegel, G., Agranoff, B., Albers, R.W., Molinoff, P. (Eds.) *Basic Neurochemistry, Molecular, cellular and medical aspects*, 4th ed. Raven, New York.
- Sokoloff, L., Reivich, M., Kennedy, C., Des Roisers, M.H., Patlak, C.S., Pettigrew, K.D., Sakurada, O., & Shinohara, M. (1977). The ¹⁴C deoxyglucose method for the measurement of local cerebral glucose utilization, theory, procedure and normal values in the conscious and anesthetized albino rat. *Journal of Neurochemistry*, 28, 897-916.
- Stephan, K.M., Fink, G.R., Passingham, R.E., Silbersweig, D., Ceballos-Baumann, A.O., Frith, C.D., & Frackowiak, R.S.J. (1995). Functional anatomy of the mental representation of upper extremity movements in healthy subjects. *Journal of Neurophysiology*, 73, 373-386.
- Stern, D. (1985). *The interpersonal world of the infant. A view from psychoanalysis and developmental psychology*. New York: Basic Books.
- Stevens, L.T. (1886). On the time sense. *Mind*, 11, 393-404.
- Stroemer, R.P., Kent, T.A., & Hulsebosch, C.E. (1995). Neocortical neural sprouting, synaptogenesis and behavioral recovery after neocortical infarction in rats. *Stroke*, 26, 2135-2144.
- Talairach, J., & Tournoux, P. (1988). *Co-planar Stereotaxic atlas of the brain*, New York: Thieme.

- Tempini, M.L., Price, C.J., Josephs, O., Vandenberghe, R., Cappa, S.F., Kapur, N., & Frackowiak, R.S.J. (1998). The neural systems sustaining face and proper-name processing. *Brain*, 121 (Pt 11), 2103-2018.
- Temprado, J.J., Monno, A., Zanone, P.G., & Kelso, J.A.S. (2002). Attentional demands reflect learning-induced alterations of bimanual coordination dynamics. *European journal of Neuroscience*, 16(7), 1390-1394.
- Thompson, J.K., Peterson, M.R., & Freeman, R.D. (2003). Single-neuron activity and tissue oxygenation in the cerebral cortex. *Science*, 299(5609), 1070-1072.
- Tillmann, B., Janata, P., & Bharucha, J.J. (2003). Activation of the inferior frontal cortex in musical priming. *Annals of the New York Academy of Sciences*, 999, 209-11.
- Tjellesen, D.G., Yurkovich, E.E., & Gragert, M. (2001). Use of music therapy and other ITNIs in acute care, *Journal of psychosocial nursing and mental health services*, 39(10), 26-37.
- Toyokura, M., Muro, I, Komiya, T., & Obara, M. (1999). Relation of bimanual coordination to activation in the sensorimotor cortex and supplementary motor area: Analysis using functional magnetic resonance imaging. *Brain Research Bulletin*, 48, 211-217.
- Treisman, M. (1963). Temporal discrimination and the indifference interval - implications for a model of the internal clock. *Psychological monographs*, 77, 1-.31.
- Turton, A., Wroe, S., Trepte, N., Fraser, C., & Lemon, R.N., Contralateral and ipsilateral EMG responses to transcranial magnetic stimulation during recovery of arm and hand function after stroke. *Electroencephalography and Clinical Neurophysiology*, 101(4), 316-328.
- Tyszka, J.M., Grafton, S.T., Chew, W., Woods, R.P., & Colletti, P.M. (1994). Parceling of mesial frontal motor areas during ideation and movement using functional magnetic resonance imaging at 1.5 Tesla. *Annals of Neurology*, 35, 746-749.
- Ugurbil, K., Toth, L., & Kim, D.S. (2003). How accurate is magnetic resonance imaging of brain function? *Trends in Neurosciences*, 26(2),108-114.

- Ungerleider, L.G., Doyon, J., & Karni, A. (2002). Imaging brain plasticity during motor skill learning. *Neurobiology of learning and memory*, 78(3), 553-564.
- Ward, N.S., Brown, M.M., Thompson, A.J., & Frackowiak, R.S. (2003). Neural correlates of motor recovery after stroke: a longitudinal fMRI study. *Brain*, 126, 1-21.
- Weiller, C., & Rijntjes, M. (1999). Learning, plasticity and recovery in the central nervous system. *Experimental Brain Research*, 128, 134-138.
- Weiller, C., Chollet, F., Friston, K.J, Wise, R.J., & Frackowiak, R.S. (1992). Functional reorganization of the brain in recovery from striatocapsular infarction in man. *Annals of Neurology*, 31, 463-472.
- Wexler, B.E., Fulbright, R.K., Lacadie, C.M., Skudlarski, P., Kelz, M.B., Constable, R.T., & Gore, J.C. (1997). An fMRI study of the human cortical motor system response to increasing functional demands. *Magnetic Resonance Imaging*, 15, 385-396.
- Wing, A.M. & Kristofferson, A.B. (1973). Response delays and timing of discrete motor responses. *Perception & psychophysics*, 14, 5-12.
- Wing, A.M. (2002). Voluntary timing and brain function: an information processing approach. *Brain and Cognition*, 48(1), 7-30.
- Wishart, L.R., Lee, T.D., Murdoch, J.E., & Hodges, N.J. (2000). Effects of aging on automatic and effortful processes in bimanual coordination. *The journals of gerontology. Series B, Psychological sciences and social sciences*, 55(2), 85-94.
- Wolpert, D.M., & Ghahramani, Z. (2000). Computational principles of movement neuroscience. *Nature Neuroscience*, 3 supp, 1212-1217.
- Xiong, J., Gao, J-H., Lancaster, J.L., & Fox, P.T. (1995). Analysis of functional MRI activation studies of the human brain. *Human Brain Mapping*, 3, 287-301.

- Yágüez, L., Nagel, D., Hoffman, H., Canavan, A.G.M., Wist, E., & Hömberg, V. (1998). A mental route to motor learning: Improving trajectorial kinematics through imagery training. *Behavioral Brain Research*, 90, 95-106.
- Yukie, M. (1995). Neural connections of auditory association cortex with the posterior cingulate cortex in the monkey. *Neuroscience Research*, 22(2), 179-87.
- Zanone, P.G., & Kelso, J.A.S. (1992). The evolution of behavioral attractors with learning: Nonequilibrium phase transitions. *Journal of experimental psychology. Human perception and performance*, 18(2), 403-421.
- Zatorre, R.J. (2001). Neural specializations for tonal processing. *Annals of the New York Academy of Sciences*, 930, 193-210.
- Zatorre, R.J., Belin, P., & Penhune, V.B. (2002). Structure and function of auditory cortex: music and speech. *Trends in cognitive sciences*, 6(1), 37-46.
- Zatorre, R.J., Evans, A.C., & Meyer, E. (1994). Neural mechanisms underlying melodic perception and memory for pitch. *Journal of Neuroscience*, 14 (4), 1908-1919.
- Zatorre, R.J., Perry, D.W., Beckett, C.A., Westbury, C.F., & Evans, A.C. (1998). Functional anatomy of musical processing in listeners with absolute pitch and relative pitch. *Proceedings of the National Academy of Sciences of the United States of America*, 95, 3172-77.
- Zysset, S., Huber, O., Ferstl, E., & von Cramon, D.Y. (2002). The anterior frontomedian cortex and evaluative judgment: an fMRI study. *Neuroimage*, 15(4), 983-91.

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Research Interests

Auditory/Music perception; perception of pitch, rhythm and affect in music; how music and rhythmic stimuli relate to motor coordination. Identification of brain areas involved in these processes using functional MRI and how this information could be used for improvement of motor control in patients with motor deficits. Currently studying the influence of rhythmic auditory stimuli on motor coordination (synchronization / syncopation modes) in Parkinson's disease patients.

Education

Currently enrolled as a full-time PhD student in the NIMH pre-doctoral program at the Center for Complex Systems and Brain Sciences, Florida Atlantic University (FAU), since fall 1998 (Advisors – Drs. Scott Kelso and Edward Large).

Master of Technology (MTech) in Biomedical Engineering; Indian Institute of Technology (IIT), Bombay, India. 1997.

Bachelor of Medicine and Bachelor of Surgery (MBBS); University of Kerala, India. 1994.

Work Experience

March 1997 - August 1998.

Scientist – Sree Chitra Tirunal Institute of Medical Sciences and Technology, Trivandrum, India. Worked in the Neurology and Biomedical departments of the institute and was involved in the development of concentric needle electrodes for Electromyography (EMG) and dural grid electrodes for Electroencephalography (EEG) and testing them on patients in the institute's neurology department.

Teaching Experience

Anatomy and Physiology: Undergraduate pre-requisite course for engineering students in the department of Biomedical Engineering, Indian Institute of Technology (IIT), Bombay, India (1996-'97); General systems physiology and anatomy of the central nervous system.

Music perception and Cognition – Fall 2002, Florida Atlantic University: Undergraduate/Graduate class – lectures on neural aspects of music processing (pitch and rhythm) in normal subjects, perception of emotion in music performance, and acquired and congenital deficits in music perception.

Computer skills

Programming languages: MATLAB, HTML, MAX

Operating Systems: UNIX/LINUX, MAC, VMS, Windows 98/2000/NT, MSDOS

Special software for fMRI analysis: AFNI, SPM

Responsible for maintaining the journal club website for the Center for Complex Systems and Brain Sciences at FAU

(<http://www.ccs.fau.edu/~nair/jc/info.html>). Developed a web-based

Neurology / Radiology journal database (KWIK SCAN -

<http://www.ccs.fau.edu/links.htm>)

Honors and Awards

1. Graduate Fellowship for academic excellence, Office of Graduate studies, FAU. 2002-'03.
2. Karen Slattery ERCCD & FAU student government award for tuition, 2002-2003.
3. Graduate grant from Graduate Grants Committee, FAU. November 2002.
4. Graduate grant from Agency for Graduate Concerns, FAU, July 2002
5. Newell Fellowship for outstanding academic achievement, Office of Graduate studies, FAU. 1999-2000.
6. NIMH pre-doctoral fellowship at the Center for Complex Systems and Brain Sciences at FAU. Fall 1998 to date.
7. Graduate Teaching Assistantship at the School of Biomedical Engineering, Indian Institute of Technology, Bombay, India. 1995-97.

Publications

1. Dinesh G. Nair, Kelly J. Jantzen, Harold Friend, Ed Kaplan, Fred L. Steinberg and J. A. Scott Kelso (in preparation). Brain networks underlying motor coordination and timing in Parkinson's disease.

2. Dinesh Nair, Armin Fuchs, Fred L. Steinberg, & J. A. Scott Kelso (in preparation). Assessing recovery in middle cerebral artery stroke using fMRI: A serial case study.
3. Dinesh G. Nair, Edward W. Large, Kelly J. Jantzen, Fred L. Steinberg & J. A. Scott Kelso (in preparation). Limbic responses while listening to music: Effects of performance expression and musical training.
4. Dinesh G Nair (in preparation). About being BOLD.
5. Dinesh Nair, Kari Purcott, Armin Fuchs, Fred Steinberg, & J. A. Scott Kelso (2003). Cortical and cerebellar activity of the human brain during imagined and executed unimanual and bimanual action sequences: A functional MRI study. *Cognitive Brain Research*, 15:3, 250-260.
6. Dinesh G. Nair, Edward W. Large, Fred Steinberg & J. A. Scott Kelso (2002). Perceiving emotion in expressive piano performance: A functional MRI study. *Proceedings of the 7th International Conference on Music Perception and Cognition*, Sydney; C.Stevens, D.Burnham, E. Schubert, J.Renwich (Eds). Adelaide: Causal Productions, pp 627-630.
7. Nair D G, Vijayan S P & Sivakumar R (2000). Evaluation of the sharpness of concentric needle electrodes by a penetration test. *Frontiers of Medical and Biological Engineering*, 10 (4): 357-364.
8. Dinesh G Nair. (1997). H-reflex recovery profile in normal subjects and cases of UMN lesions. *Master of Technology Thesis*, School of Biomedical engineering, Indian Institute of Technology, Bombay, India. January 1997.

Abstracts

1. D.G. Nair, A. Fuchs, F.L. Steinberg, & J.A.S. Kelso (2003). Assessing recovery from stroke using functional MRI: A serial case study. Program No. 823.6. 2003 Abstract Viewer/Itinerary Planner. Washington, DC: Society for Neuroscience.
2. D.G. Nair, E.W. Large, F.L. Steinberg, & J.A.S. Kelso. (2002). Emotional communication in music performance: A functional MRI study. Program No. 381.1. 2002 Abstract Viewer/Itinerary Planner. Washington, DC: Society for Neuroscience.
3. D.G. Nair, E.W. Large, F.L. Steinberg, & J.A.S. Kelso (2002). Emotional communication in music performance: A functional MRI study. Abstract, NIMH symposium, X Dynamical Neuroscience, Orlando, Florida.

4. Dinesh G. Nair, Edward W. Large, Fred L. Steinberg, & J. A. Scott Kelso (2002). Perceiving emotion in expressive piano performance: A functional MRI Study. Abstract: Coordination Dynamics, International Conference on Brain and Behavior, Delray Beach.
5. D. G. Nair, K. L. Purcott, J. M. Mayville, A. Fuchs, F Steinberg & J. A. S. Kelso. (1999). Comparing motion and imagery related brain activation- a functional MRI study. Abstract: NIMH Symposium of Dynamical Neuroscience VII, Delray Beach, Florida.
6. A. Fuchs, K. L. Purcott, D. G. Nair, J. M. Mayville, S. Owens, F. Steinberg & J. A. S. Kelso. (1999). Brain activity in perception-motor coordination, revealed by functional MRI. Abstract: NIMH Symposium of Dynamical Neuroscience VII, Delray Beach, Florida.
7. Dinesh Nair, Suresh Devasahayam & T. Sreedhar. (1997). H reflex recovery profile in normal subjects and cases of UMN lesions. Proceedings of the Silver Jubilee Annual National Conference of Physical Medicine and Rehabilitation, Jaipur, India.

Student memberships in professional societies

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