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École polytechnique de Louvain

Fingerprint of Essential Tremor in motor control

Author: **Florence BLONDIAUX**
Supervisor: **Frédéric CREVECOEUR**
Readers: **Bernard HANSEEUW, Louisien LEBRUN, Philippe LEFÈVRE**
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Abstract

The pathophysiology of Essential Tremor (ET), the most common movement disorder, is not well understood. Evidence points towards an implication of the cerebellum in the generation of movement oscillations. Recent theoretical work showed, on the other hand, that oscillations could arise from an erroneous estimation of transmission delays, inherent to the conduction of neural signals. This process of sensory delay estimation is often assigned to the cerebellum. These two findings prompted us to investigate the fingerprint of Essential Tremor on motor adaptation, a task known to involve the cerebellum and which depends on delayed sensory feedback.

We performed two motor adaptation tasks, focusing on saccadic and upper limbs movements, with a group of ET patients and a group of aged-matched controls. Patients with ET appears to have limited abilities to adapt their movements in response to perturbations, and this impairment was correlated with the intensity of the tremor.

This motor adaptation impairment could be a new behavioral marker of the disorder and could bring novel possibilities for diagnosis, including a quantitative way to assess the patient's disorder, and new perspectives for rehabilitation. Further research is needed to validate these findings. However, the encouraging results obtained with the two experiments will pave the way for further investigations in the field, particularly on tasks involving the sensory feedback loop, which is suspected to play a major role in the generation of Essential Tremor.

Contents

Chapter 1

Introduction

Our knowledge about neurological disorders drastically increased in the last few decades, improving our abilities to understand, diagnose, and treat many patients, and therefore increasing their quality of life. However, some disorder remained out of the focus of research and are still a mystery to solve.

This is the case of Essential Tremor, the most common movement disorder. Essential Tremor patients are affected by a tremor, mainly during action and postural conditions and the tremor is present in most cases for the upper limbs, head and face. This disorder can have heavy consequences in daily life activities. Unfortunately, the causes of this tremor remain unknown, and the treatments currently used for this pathology show limited results and are not effective for all patient or for a long time. Understanding the root causes of this movement disorder would play a key role in making more accurate diagnoses, and exploring new paths for more effective treatments.

To explore the role the cerebellum plays in this disorder, I conducted two experiments with a group of patients and a group of controls, investigating their abilities to learn in new environments. Two tasks were selected, a saccadic adaptation experiment and a hand reaching task.

These experiments suggested that patients' abilities to adapt to new arm and eye dynamics are impaired in comparison with the control group. These abilities are known to be impaired when the cerebellum is damaged and evaluating patients' abilities in this kind of condition might shed a different ligth on the disorder.

The main question we want to investigate with this thesis is: Is the motor adaptation abilities of patients with Essential Tremor impaired ?

We know that the origin of the tremor lies in the cerebello-thalamo-cortical loop,

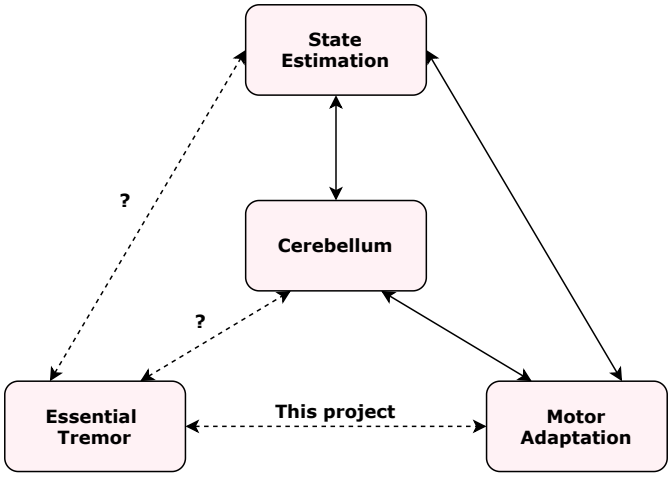


Figure 1.1. The four principles on which our hypothesis is based

but more exact mechanisms responsible for the tremor remain unknown. On the other hand, recent theoretical work showed that a false estimation of the transmission delays, inherent to the conduction of neurological signal through the nerves, often assigned to the cerebellum, can lead to oscillations with the same properties as the tremor of ET patients. [1] These two statements prompted us to investigate the fingerprint of Essential Tremor on motor adaptation.

The principles driving this project and their interactions are summarized on figure 1.1. Motor adaptation is a mechanism that is known to be dependent on the state estimation and on the integrity of the cerebellum (solid lines). Theoretical work has shown that an inaccurate delay estimation, potentially within the cerebellum, leads to oscillations. This makes the cerebellum a likely candidate for the generation of the tremor (dashed lines). Finally, this project will investigate the abilities of Essential Tremor patients to perform motor adaptation tasks. Identifying a deficit of motor adaptation would support the implication of the cerebellum in the generation of Essential Tremor.

Chapter 2

State of the art

The three main pillars supporting our hypothesis and their implication with the cerebellum will be briefly explained here. I will begin by outlining Essential Tremor, state estimation and motor control and I will conclude with a brief explanation of motor adaptation.

2.1 Essential tremor

Essential tremor (ET) is one of the most common movement disorders, affecting 5% of individuals above 65 years. [2] [3] Motor and non-motor symptom variability between patients are making the diagnosis and study of the origin more complicated. The involvement of the cerebello-thalamo-cortical loop is confirmed but the exact mechanism from which the tremor emerges remains unknown.

2.1.1 Definition of Essential Tremor

No consensus is found in the literature about the definition of Essential Tremor. We have to keep in mind that ET is a syndrome and not a specific disease. The difference between a disease and a syndrome is that for a disease, we have a particular abnormal condition from which symptoms emerge compared to a syndrome that is defined by a set of symptoms that are correlated with each other but that do not refer to a particular disease. [4]

When evaluating the tremor, 3 conditions are usually observed, at rest, when the limb is fully supported against gravity, in the postural condition, when the person

maintains a position against gravity, for example, arms stretched and in the action condition, with voluntary movement of muscles. Several definitions exist for ET, but they sometimes conflict with each other. The term "Essential Tremor" was first used by Burresi in the late 19th century to describe patients that had an action tremor without any other neurological signs. However, since this first usage the definition of ET has evolved. In 1983 Marsend et al. defined 4 types of Essential Tremor: [4]

- Type 1 ET: Mild hand tremor, produced by high adrenaline (hyperadrenergic) states like stress, drug withdrawal,... The frequency of the limb's oscillations depends of the inertial loading of the hand.
- Type 2 ET: Additionally to hand tremor, this type often also includes head, voice or lip tremor. It is more severe than type 1 tremor, and its frequency does not dependent of the inertial loading of the hand. The tremor is produced by a central neurogenic oscillation. This kind of tremor is often disabling, but most of the patients have not been diagnosed by a practitioner. The typical frequency ranges from 4-8 Hz.
- Type 3 ET: Severe and disabling tremor, it can be the natural progression of type 2 ET but it is not always the case. The frequency is slightly lower than for type 2: 4-6 Hz.
- Type 4 ET: Non-specific action tremor mainly of the upper limbs. Believed to be secondary to another disease, such as dystonia, Parkinson's disease,...

Since this first classification, further work has been done to define the syndrome. A new classification has been published in 2017 by the International Parkinson's and Movement Disorders Society. ET is defined as an isolated tremor syndrome, affecting both upper-limbs during action, lasting for at least 3 years, with or without tremor of the other limbs. In addition to this definition, the ET-plus category has been introduced for patients presenting, in addition to the ET definition, other symptoms such as dystonic posturing, rest tremor, or non-motor symptoms such as mild memory impairment or other mild neurological symptoms of unknown cause. [5]

Tremor is an involuntary oscillatory movement of one part of the body. Oscillations can have 2 origins, superimposing each other : the mechanical-reflex oscillation and the central-neurogenic oscillation.

The larger oscillation is due to mechanical-reflexes, it represents the response of the limbs to pulsatile perturbations and its frequency is governed by the inertial and elastic properties of the body. This tremor triggers the somatosensory receptors but their response is usually too weak to entrain motoneurons at the frequency of

the tremor, and therefore is not noticeable on EMG. Type one ET is consistent with this definition, however, it is in conflicts with the findings that ET is produced by a central neurogenic oscillation, therefore, type 1 has been excluded from the definition of essential tremor. [4]

The second kind of tremor is the one characterizing ET patients, which is consistent with the supposed origin of their tremor. The central-neurogenic oscillation component of the tremor is driven by the rhythmic modulation of the motor-neuron activity. This oscillation is relatively independent of stretch reflexes and limbs mechanics and therefore is independent of the loading condition. Due to its properties, the oscillations in this case are believed to originate from an oscillating neural network. A rhythmic entrainment of EMG is observed in the case of this tremor. [6]

Observations with ET patients reported a tremor frequency in the range of 4-12 Hz. [4, 7] The frequency of the tremor tends to decrease with years leading to an increase in tremor-amplitude due to the low-pass filtering properties of the muscles. A longitudinal study focused on the tremor's frequency of 40 ET patients, over a 10-years period. The results showed that the tremor frequency tends to decrease by 0.12+- 0.04 Hz per year. [8]

One team conducted several studies on muscle contraction patterns of ET patients, using surface recordings of muscles activity (EMG) during rest and postural tasks. [7, 9, 10] During their studies, they observed that those contraction patterns for antagonist muscles were mostly in phase with each other during the rest condition. If the contraction of antagonist muscles are in phase, they will cancel each other action. In contrast, during the postural condition contractions were usually out of phase, resulting in a stronger tremor than at rest. By coupling EEG and surface EMG they showed that ET patients exhibit a stronger synchronization of motor units, reflecting that they share the same central drive, at the tremor frequency. This supports the hypothesis that the tremor emerges from the cerebello-thalamo-cortical loop.

In addition to the motor impairment, most ET patients also shows cognitive impairments. Clinical studies focus more and more on non-motor impairments in ET, for example dementia. Cognition has been studied a lot, but similar to the studies on motor impairments, there is poor documentation on the evolution over time. ET patients have an increased incidence of mild cognitive impairment and dementia. The cognitive functions believed to be imparted are theory of mind, verbal fluency, mental set shifting, inhibition and problem solving. These deficits could be explained by the result of an alteration of the cerebellar-cortical networks, in particular the one projecting to and from the prefrontal cortex. Those results

must be taken carefully due to the low number of studies and longitudinal studies on the subject. [11]

2.1.2 Pathophysiology of ET

ET is a heterogeneous disorder (a disorder which have several etiologies). Previous neuroimaging and pathological studies have produced heterogeneous results. The main reason for this is the significant number of misdiagnosis that there is for this pathology. Indeed, an ET diagnosis is often given when all other pathologies causing tremor can be ruled out. Unfortunately at an early stage of the disease, the symptoms of PD and ET overlaps and providing an accurate diagnosis is difficult. [12] Around 40% of the patients who participated in a previous study received a different diagnosis when consulting a new center. [13]

Within ET patients, there is some heterogeneity, in the site of the tremor, in the non-tremulous symptoms (cognitive symptoms,...) and the drugs effective for their specific tremor. Theses heterogenities might indicates different ET subtypes but no consensus has been found on this point.

Three main (nonexclusive) hypotheses exists on the possible etiology of the tremor:

The neurodegeneration hypothesis

The neurodegenerative characteristics of the disorder have not been established yet. The arguments in favor of the hypothesis state that the tremor follows a progressive course and is associated with age, and some studies showed ET patients have increased risks of contracting Parkinson's disease and Alzheimer's (two degenerative disorders). Opponents of the hypothesis point out that many findings about pathological abnormalities have not been reproduced and that some of them do not correlates with the duration of ET. [12]

During the pathological studies, evidences has been gathered for cerebellar disease. But most of these studies have been conducted on a small number of patients. The main structural changes observed in postmortem studies are modifications of Purkinje cells axons and dendrites. The number of axonal swelling and thickenings of the unmyelinated portion of the axons (Torpedoes) were significantly higher than the amount of Torpedoes present in the cerebellum of aged-matched controls. These Torpedoes are similar to the ones observed in response to other cerebellar diseases. A significantly increased number of dendrites swellings have

been observed in ET patients' cerebellum in comparisons to healthy controls. [14] A lower average number of cerebellar Purkinje cells, 25% less than controls, have been observed in ET patients' brains, a result that could be associated with a cerebellar disease. [14, 15]

Structural neuroimaging studies found abnormalities of both grey and white matter in the cerebellum of ET patients. However a large variety of results have been observed. [2] [3] Depending on the location of the patient's tremor, volumetric abnormalities have been found at different places in the cerebellum, coherent with the somatotopic organization of the cerebellum and the patients' tremor location. [16] Findings that have been confirmed by a postmortem study.

The GABA hypothesis

This hypothesis states that ET is associated with abnormal function of the inhibitory neurotransmitter GABA. A first element in favor of this hypothesis is the efficacy of drugs that increase GABAergic transmission. The reduced level of GABA found in the cerebrospinal fluid of ET patients constitutes a second element in support of this hypothesis. Additionally, studies on animals showed similarities with ET postural tremor when manipulating the GABAergic transmission. An experimental inhibition of the GABA-A receptors, using harmaline, provokes a tremor similar to ET. Another element in favor of this hypothesis comes from a PET study which showed reduced GABAergic function in the cerebellum, ventrolateral thalamus and lateral pre-motor cortex of ET patients. [2] The location of the GABAergic transmission reductions coincided with the location of the neurodegenerative changes. Finally, a postmortem study showed a reduction in the levels of GABA-A (35%) and GABA-B (22-31%) receptors compared to controls. [12]

The functional network hypothesis

Previous research focused a lot on finding the single oscillators driving the tremor. This research was based on the idea that a hyperpolarization of some neurons generates oscillations independently at a given frequency. However, this theory has been falsified in the last few years, first because studies showed that many oscillating patterns were only intermittently coherent with the tremulous muscle activity. Secondly, deep brain stimulation studies have highlighted that several spatially separated tremor clusters are capable of driving the tremor. Because of these findings, the focus turned to network properties. Investigating the strength and directionality of interregional connectivity. Following this hypothesis, all the

components of the network would act as oscillators, dynamically entraining each other. [12] PET studies described a bilaterally increased activity in the cerebellum during simple postural tasks which has been confirmed by fMRI studies showing increased activity in the cerebello-thalamo-cortical loop. [2]

It is known that tremor implies oscillations in the cerebello-thalamo-cortical loop. In a previous study it has been shown that in healthy patients, there is a unidirectional signal flow in the thalamo-cortical pathway, but in ET and parkinsonian subjects, this flow is bidirectional. Healthy controls (HC) have been asked to mimic the tremor to compare the activation with ET patients. The activation in the cortical region is the same for both groups but the cerebellar sources mapped to the sensory motor cortex for ET patients while mapping to the premotor cortex for HCs. The activity flow for impaired subjects was mainly from cerebellum to cerebral cortex rather than for HC which showed the opposite direction. [17]

Recent studies investigated the relationship between the dentate nucleus connections and the motor and non-motor symptoms in ET. The dentate nucleus being the main output cerebellar pathway, an important region for the regulation of many aspects of voluntary motor activity and for many cognitive cortical functions. Patients' tremor severity was assessed using the Fahn–Tolosa–Marin tremor rating scale (FTM-TRS). ET patients showed significantly reduced dentate nucleus functional connectivity with both cortical and subcortical brain areas. Results were negatively correlated with the FTM-TRS score, meaning weaker functional connectivity was related to more sever tremor. Some regions were also correlated with patients' cognitive profile, lower functional connectivity was linked with worse cognitive performances. [3]

Key elements about ET

- Mainly kinetic and postural tremor.
- Affecting more commonly the upper limbs but also the head, face, voice, trunk and lower limbs.
- Range of the tremor frequency is 4-12 Hz and is independent of the loads added to the limb.
- Origin is unknown but empirical evidence suggests that the cerebello-thalamo-cortical loop is involved in the generation of the tremor.
- The three main nonexclusive hypotheses about the origin of the tremor are : a neurodegeneration, a GABA receptors anomaly, and an anomaly of the functional connectivity.

2.2 State estimation and motor control

We are able to perform complex daily life activities, like grasping a cup of coffee with one hand while reaching for the phone with the other hand or playing tennis with a friend. When we play, we have to decide from which angle we will hit the ball, at which speed,... All of these decisions have to be made in a dynamic environment that changes over time, the cup might be more heavy than we expected or the phone more slippery. We have to adapt to these new conditions in order to perform the desired task.

We are able to produce fast and well coordinated movements. In order to do so, we need to select the motor commands that will guide us to our goal. This cannot be achieved by pure feedback control because sensory feedback is subject to significant time delays. Therefore some computations have to be done to compensate for those delays. [18]

The first idea specific to optimal control emerged in the 80s, hypothesizing that motor commands are selected in a way that minimizes certain parameters such as the hand acceleration, the torque change or the energy consumption. This idea has been pushed further including the sensory feedback and can be described in the optimal feedback control (OFC) framework.

2.2.1 Definition of the system

The problem can be captured as a system. A dynamic system that can be characterized by a state at each time step. The state being the joint(s) angle(s), velocity(ies),... A controller can influence the state of the system by influencing the control vector. In our case, varying muscle activity, this control vector will influence the state following a specific function that takes into account the dynamics of the body. To go from point A to point B, there is a multitude of movements possible, how do we select one? The optimal control vector will be selected minimizing a cost function.

Several factors that are not under our control can influence our movements. The activation of the neural circuits is variable and therefore introduces variability in motor behavior. Additionally, there is neural noise in the sensory systems, movement preparatory activities and in the activation of muscles. And finally external perturbations can also generates motor errors. Therefore the system needs to take this into account and uses the sensory feedback to update its motor command to achieve the desired goal. [19]

Various types of sensory feedback exists, it can be visual, helpful to perceive our environment or it can also be feedback from cutaneous receptors, useful to perceive tactile information, to obtain information of contact between our skin and the environment. And finally muscle afferents, that plays a crucial role in movement as contracting our muscles is our way to interact with our environment. [20]

A traditional view of motor control was the combination of inverse and forward models that have been introduced very soon to explain our abilities to achieve some desired trajectory, and to overcome time delays that are associated with feedback control.

Two kinds of internal models were defined, the forward model that predicts the next state based on the current state and the motor command while the inverse model, based on the desired and current states, predicts the motor commands needed to get there. [18] The role of feedback pathways in this framework being unclear, these concepts were translated to the framework of Linear–quadratic–Gaussian (LQG) control to include closed loop control and state estimation.

2.2.2 Optimal feedback control

A way to cope with this dynamic environment and with the complexity of our movements is the optimal control framework, which can be observed in figure 2.1. It can be divided into 3 big axes: The task selection, the controller and the state estimator.

Task selection

The task selection can also be considered as the "What", it represents the overall objective that we decided to achieve. This voluntary decision can be a simple action or a series of complex motor actions. [20]

In order to decide which motor commands are the most suitable, we need the controller.

Controller

Based on the task and the estimation of the current state of the system, we need to choose the optimal control vector, within the multitude of motor commands that will bring us to the desired state. The controller represents the "How" of the

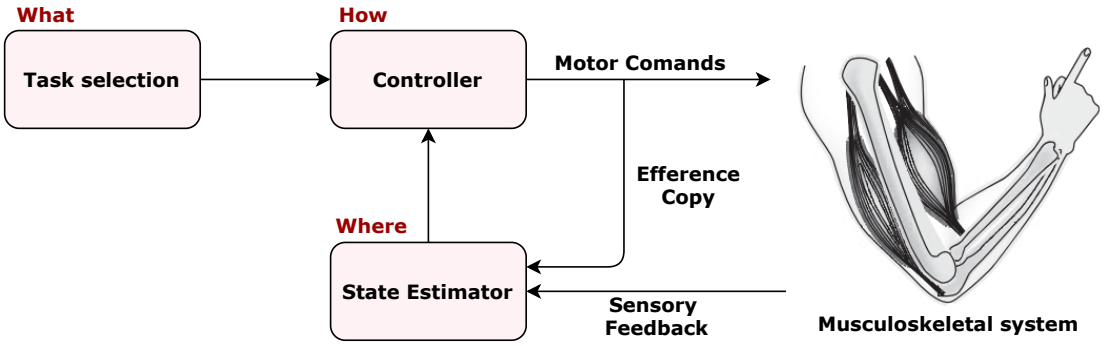


Figure 2.1. Schematic representation of the processes under the optimal feedback control framework (OFC). Task selection will determine the feedback control policy. Motor commands are sended to the peripheral musculoskeletal system. An efference copy of the motor commands is used in combination to sensory feedback to predict the consequences of motor actions. The internal predictions are used to compute the posterior estimate of the state of the limb. The estimated state will be used to adjust the motor commands of ongoing motor actions. Figure adapted from [19]

movement, how will we select the best motor commands. OFC represents quite well the motor system as it does not assume that grasping a cup of coffee always correspond to the same set of motor commands, it depends on the current state and environment and takes the feedback into account. Reaching your cup during the coffee break at work or on a boat in the middle of a rough see won't require the same motor commands. [21]

The optimal control vector will be obtained by minimizing a cost function representing the system, the cost function depends on the state and the control vector and will take into account the constraints on the state variable and how the motor commands are penalized to reach the goal. [19, 22]

To make an analogy with the internal models, the controller plays the role of an inverse model, taking the desired state, the expected current state and the constraints, represented by the cost function, to generates the optimal set of motor commands.

One of the main challenges of this controller is to obtain the estimation of the state. Therefore, the last main axis of the OFC framework is to compute an optimal estimate of the state, as depicted on figure 2.1.

State estimation

The state estimation step defines the "Where" of the system, where are our limbs, what is the current state of the body. It is not an easy task, the exact state will never be known, indeed, motor noise is present in the delayed sensory feedback. The state estimator estimates the current state based on the delayed sensory feedback and the efferent copies of commands sent to the muscles. An estimated state, is needed by the controller to select the most appropriate control commands to reach the desired position under the defined constraints.

All these delays can induce instability in the system, especially when initiating corrective responses or fast movements, delays needs to be compensated. One way to do so would be to predict the expected state of the body using the efferent copy of the motor commands. Internal forward models, that represents the dynamics of the body, allows us to predict the consequences of such the motor commands based on the last estimated state. This estimation would be efficient if there were no uncertainties in the system, but internal models are not always correct, and this technique does not account for, nor respond to, external perturbations. [20]

In order to detect and respond to perturbations, the sensory feedback needs to be integrated along with the internal prior into the state estimation process. If no compensation is made for the delays of this feedback, the corrective responses will be inefficient as the corrective motor commands will always be based on a delayed state. They will even in some cases lead to instability in the system. [22]

The estimated state of the body will be a combination of the internal feedback estimate, the prior knowledge, based on the efferent copy of the motor commands and the external sensory feedback estimate, an estimation of the state from the sensory feedback with a compensation for the delay. [20]

Previous models have shown that the brain uses nearly optimal estimates of the current state by combining prior knowledge and sensory feedback in Bayes-optimal fashion. This Bayesian framework is particularly useful to take into account the uncertainty we have about the environment and the nervous system. Using a Kalman gain, it specifies how much we should rely on the available sensory data when updating our prior estimate. [19]

Previous techniques often tackled this problem by performing, after a discretization, system augmentation to compensate for the delays. Once the delays are compensated, Bayesian integration of prior knowledge and estimated feedback is performed. Unfortunately, it seems unrealistic that biological systems preserve all the present and past estimates that are required for system augmentation.

In order to investigate the consequences of an inaccurate delay compensation, a recent study by Crevecoeur et al. [1], showed that probabilistic filtering of the predicted state can compensate for predictions errors like delay mismatch between the plant's delay and the expected delay or errors due to a low dimensional approximation of the system. To reduce the computations, the dimension of the system can be reduced by discrete time intervals.

First, the system needs to extrapolate an estimation of the current sensory feedback based on the delayed feedback. It can be solved like a boundary value problem, with uncertainty on the initial condition. The delay will be compensated by integrating the control vector over the delay interval.

The one-step prediction of the state can be obtained by predicting the consequences of the motor commands on the previously estimated state over the discretization interval. We can consider that the motor command is constant over one time step.

Finally, using the expression of the conditional distribution of Gaussian random variables, the one-step prediction and the extrapolated feedback state, can be combined to design our probabilistic filter. This filter is a natural extension of a Kalman filter.

All the steps described above can be performed by simple operations, matrix multiplications and additions, averaging and low-pass filtering. Operations that can easily be implemented in the neural circuits. [1]

2.2.3 Effect of a delay mismatch

If the true delay of the system does not match with the estimation of the delay the state estimator uses, the compensation won't be optimal and errors will be observed. However, in our biological systems, assuming that the delay used for compensation will always match with the delay of the plant is not realistic. Therefore errors must be contained.

Simulations have been done by Crevecoeur and colleagues to observe the consequences of a delay mismatch on eye and hand movements.

The results are shown on figure 2.2. For the saccades, two configurations have been selected. In the first configuration, the delay is underestimated, and the middle panel represents the situation where the delay is overestimated. It can be seen that when the delay is underestimated, there are overshoots in the movement, the true state is always ahead of the estimated state, the corrective responses are not appropriated. Conversely, overestimating the delay leads to undershoots.

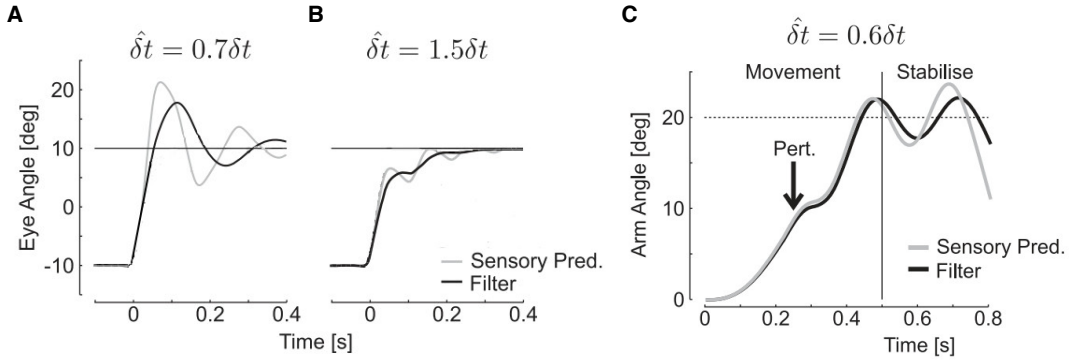


Figure 2.2. Simulations of a delay mismatch for eye (a,b) and hand (c) movements. The delay is either underestimated (a,c) or overestimated (b). Grey lines represent a state estimation based only on the sensory prediction while black lines represents a state estimation based on the filtered sensory prediction. Adapted from [1].

Filtering the prediction (black lines) is efficient to reduce the consequences of delay mismatch. If the estimation is only based on the sensory feedback (gray lines) the overshoot and oscillations are greater and can even lead to instability in the system, as seen on the right panel for upper limb control. The results show that filtering reduces the impact of prediction errors. Even with some errors, the system can be stabilized. [1]

In order to characterize the oscillations observed when the delay is underestimated, a last task was performed. The controller had to maintain the limb at the origin and keep the position despite the small perturbation applied to it. The task was repeated across a range of different load conditions. Results are available in fig 2.3. The peak in the power spectral density happened at approximately the same frequency for the three loading conditions and for the different underestimations of the delay. The oscillations are independent of the loading condition. If no compensation for the delay was realized, the system diverges to infinity for all movements and in all cases. [1]

The oscillations observed during these simulations are somewhat reminiscent of the ET patients' tremor. Oscillations only occurs during postural and action conditions as they suggest a problem in the state estimation step. Their frequency is similar, around 4-5 Hz, and is independent of the loading condition, as observed in ET. An inaccurate estimation of the delay could actually come from a miscalibration of the averaging or filtering operations in the cerebellum.

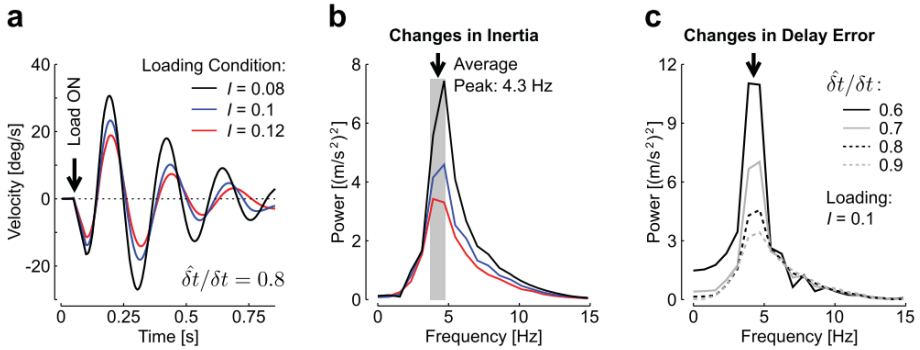


Figure 2.3. Simulations of movement oscillations across different loading conditions and delay underestimations. The controller had to keep the limb still despite the perturbation applied on it. Adapted from [1]

Key elements about motor control

- Since the importance of sensory feedback has been clearly established, the theory implies that there must be a mechanism that compensates for delays.
- Internal models of the body dynamics can help to compensate for these delays and to generate a prior estimate of the state of the system
- Sensory feedback and prior knowledge must be integrated together to compensate for the delays and the uncertainties of the system
- The optimal motor commands can be selected by minimizing the cost associated with them
- Inaccurate estimations of the sensory feedback delays can lead to oscillations
- These oscillations shows similar properties as the oscillations observed with ET patients

2.3 Motor adaptation

We are able to correct our movements in responses to perturbations but what will happen if this perturbation is constantly there, if we are moving in an environment with a new dynamic. With time, we are adapting our movements to the novel environment in order to reduce the error. The errors driving this learning are not only errors at the end of the movement, all the errors resulting from a mismatch between the predicted state and the state extrapolated from the sensory feedback are involved. This adaptation can be done by an adaptation of the internal models described earlier. [23] Indeed, a typical behavior is to exhibit large errors with strong corrective actions at the beginning. After a couple of movements in the environment, the errors are reduced and the movements are more and more similar to the movements in the previously known dynamic. Once the perturbation is removed, subjects shows after effects of the new dynamics learned. After effects that will vanish with time. [24] A classic way to look at upper limbs adaptation is to perform movements towards a target with a robotic arm that can apply forces to the limb.

One of the first force adaptation studies focused on the adaptation of subjects performing movements in a force field. Strong deviations from the optimal path were observed immediately after the introduction of the force field. After a few movements, the deviation decreased and the movements were similar to the movements during the no field condition. The correlation of the velocity profiles with and without the force fields increased with learning. The strong after effects that were observed when the field was removed are consistent with the hypothesis that an internal model is created or adapted for this environment. [25]

2.3.1 Mechanisms behind motor adaptation

When moving in a new environment, our motor commands might not always be exact, resulting in an error during and at the end of the movement. Aiming to reduce the error, we might act on the source of the problem and adapt our internal models to correct the motor commands. Considerable improvement of our performances can be observed within tens to hundreds of trials. [26] The rate to which these models adapt can be different. In 1999, in order to explore this aspect Brushan et al. modeled goal-directed reaching movements in a force field. At that time, motor control was explained by the forward and inverse models, that have been remodeled since that time into the LQG framework. A constraint was imposed on the adaptation rate of the internal models, only one of two models could adapt at a time. Significant improvement of performances was observed

when only the forward model adapts. Conversely, if only the inverse model adapts, simulations showed more moderate improvement of performances. A reaching experiment with subjects confirmed a quicker adaptation of the forward model in comparison to the inverse model. [27]

In order to properly model our abilities in terms of motor learning, a model based on at least two timescales is needed. The two components needed to model properly our abilities are a model that responds poorly to error but with good retention, and one with rapid response to error but a high forgetting. This two-timescale model would explain our saving abilities, namely, why we are able to relearn a task faster than during the initial learning. This model would also explain our rapid de-adaptation abilities, namely, why we forget faster than we learn.

In the two timescale model, learning depend on the fast and slow model, the fast state will contribute a lot in the beginning, reducing the error quickly while the slow model will slowly learn, when removing the perturbation, the fast model will respond quickly to correct the new error but the slow model will be biased towards relearning which explains our abilities to relearn faster. Even if the slow adaptation module is slow, it plays a major role in short-term motor adaptation tasks. [28]

The uncertainty about the perturbation must be taken into account, indeed, intermittent errors, like muscle fatigue, should be quickly corrected but also quickly forgotten whereas errors present for a long time, like changes in dynamics due to a disease, should result in slow adaptive changes. Many possible perturbations timescale exists and will influence our behavior, which timescale is the most likely? Baysian statistics captures this uncertainty by estimating the contribution of the two timescale and their uncertainties in response to the outcomes of the motor commands. [29]

Beside this multi-timescale adaptation, recent findings suggested a very fast adaptation timescale, of around 250ms. In addition to the trial-by-trial adaptation described above, evidences points towards an adaptation of the internal representations within the trial. Previous studies assumed that the internal representation used to control the movement was fixed during its completion, and that the adaptation was only at the end of the trial. But evidences showed that the fast timescale adaptation could complement control mechanisms. Adaptive control would take place in parallel of the control loop, tuning its parameters depending on the limb and environment properties while monitoring for model errors. [30] This model could explain the after-effects that are observed when the environment is changed, including when the force field is turned off during the trial. [26]

2.3.2 Cerebellar integrity and motor adaptation

Cerebellar damage impairs adaptation in many movements: reaching, walking, eye movements and postural control. Many experiments have shown that patients with cerebellar damages show impaired abilities for motor learning. [23, 24, 28, 31–36] Many studies demonstrated that the cerebellum plays a crucial role in state estimation. For example, an experiment was realized with a group of controls and cerebellar patients, they had to hold a basket by a force transducer measuring the grip force. First, the experimenter was releasing a ball in the basket, which pulls the hand downwards and the subjects will squeeze the basket more to avoid slipping. All the participants exhibited a delayed response, due to the delayed sensory feedback. Then the subjects were releasing the ball themselves, the controls were anticipating the consequences of their actions and squeezed the basket handler around the time the ball was released while the cerebellar patients continued to show a delayed response. [23] A similar experiment was conducted on occulomanual tracking in non-human primates. Animals' had to look at targets moving on a screen and their eyes position was recorded. Animals' performances were evaluated in two conditions they had to follow first an external target printed on a screen and secondly their hand served as a visual target. Without any lesions, the animals were showing more saccadic movement when following the external target. Indeed, sensory feedback is impacted by long delays, and visual feedback is needed to follow the external target, predicting the following path of the target was not possible. To stay on the track of the target with delayed information, the eye will have to effectuate saccades towards the last position obtained by visual feedback, resulting in saccadic movements. Conversely, the eye movements became smoother when following their own hand as they were able to use the efferent copy of their hand motor commands to predict of the consequences of their actions. Animals with a cerebellar lesion obtained the same results as controls animals when they were following the external target. However, when following their own hand, eye movement exhibited a larger proportion of saccades in comparison with controls animals, as if they were not able to predict or use the consequences of their motor commands. [31] In an experiment performed with humans, Miall and colleagues found that transcranial magnetic stimulation of the cerebellum, can be used to alter the state estimation abilities of healthy controls. [35]

Thus, these elements among various others points that the cerebellum is involved in the state estimation and motor adaptation process.

Key elements about motor adaptation

- Motor adaptation is an error-driven form of learning
- It lies over several timescales, fast, medium and long depending on the nature of the skill learned / the perturbation compensated
- Impairment of the cerebellum usually implies impaired motor adaptation

2.4 Our work in this framework

One basic premise of this work rests upon the idea that there is an intimate relationship between estimation and adaptation. Estimation requires internal models and adaptation is the process by which these internal models are updated. The tremor of patients with ET could be generated by errors in state estimation and therefore we suspect that adaptation might be altered as well. Based on this hypothesis, we chose 2 motor adaptation tasks involving the cerebellum : upper-limb and saccadic adaptation.

Chapter 3

Saccade Adaptation

This task is inspired by the work of Xu-Wilson and colleagues on adaptive motor control of saccades. [34] During this saccade adaptation task, subjects are instructed to look at targets on a screen. During the movement, the targets jump to a new location on the display. Subjects will slowly adapt their eye trajectory in anticipation of the target jump.

3.1 Method

Subjects 17 patients registered for the study, all were diagnosed with Essential Tremor. To confirm the diagnosis, a neurological assessment of their syndrome was conducted, using the Fahn–Tolosa–Marin tremor rating scale (FTM-TRS). The scale is available in Appendix 5. If any doubts existed about the diagnosis, we excluded the patient from the study. The group kept for analysis consisted of 14 patients (9 female and 5 male), with an average age of 60 years (age range 28-86).

The FTM-TRS scale is divided into 3 categories, first a tremor assessment evaluating the tremor of every limb, trunk, tongue and head in 3 conditions (if possible depending on the body part), at rest, in the postural (limb maintained still against gravity) and in action condition. The scale also contains a drawing/writing assessment and a questionnaire on daily life activities. To obtain a score that reflect as much as possible ET patients' reality, the scores kept for the following analysis are the tremor score of the upper limbs (max 24) and the drawing/writing assessment (max 32). A justification of this selection of criteria can be found in the discussion, chapter 5.

An aged-matched control group was being recruited few days before the COVID-19 situation, therefore, most of the appointments have been canceled and only 4 controls took part in the experiment. As soon as it will be possible, we will continue the experiment and recruit the 10 missing controls. The group for the analysis is composed of 4 healthy controls (3 females, mean age 53, range 27—68). The tremor assessment was also performed with the controls to exclude participants with a tremor from the control group.

Experimental set up and design Subjects sat in a dark room, their head on a chin rest. Several 0.8° targets were printed on a black screen located 1,57 meters in front of the subjects. Horizontal and vertical eye movements were recorded using a tower mounted Eyelink II recording system. The raw eye position was recorded at 1000 Hz and saved on a computer for offline analysis. For the analysis, the raw positions were filtered with a low-pass filter using a cutoff frequency of 200Hz.

The experiment was divided into 3 types of saccades summarized in fig 3.1. The three conditions are oblique, horizontal and adaptation trials, and participants performed 390 saccades in total. During all conditions, the trial began by fixing the fixation target, F. The first block consisted of a series of 30 oblique saccades, for which the target was presented at an oblique angle. The second block consisted of 30 horizontal trials where the target was presented 20° to the right of the fixation target, at the same height. After these two first small blocks, the adaptation trials were presented in 5 blocks of 60 trials, resulting in a total of 300 adaptation saccades. During the adaptation trials, the subjects were fixing the target F when a new target, T1, appeared 20° to the right. As soon as the subjects initiated their saccades, the target jumped 5° vertically at a new position T2. The first saccade, towards T1 ended with an end-point error as the target position changed. A corrective saccade was needed to get from T1 to T2. In order to reduce this end point error, subjects adapted their motor commands to end their movement closer to T2. The adaptation therefore took place in the vertical direction. This data analysis will only focus on the characteristics of the first saccade. T2 became the new fixation target for the next trial. Jumps always occurred counterclockwise. The experiment ended with a block of 30 horizontal trials, identical to the second block.

Data analysis Saccade start and end were detected by a 16°/sec speed threshold. In addition, 3 criteria must be fulfilled to include the saccade: (1) Saccade amplitude must exceed half of the target displacement. (2) Saccade duration must lie between 50 and 200ms. (3) The peak horizontal velocity must be greater than

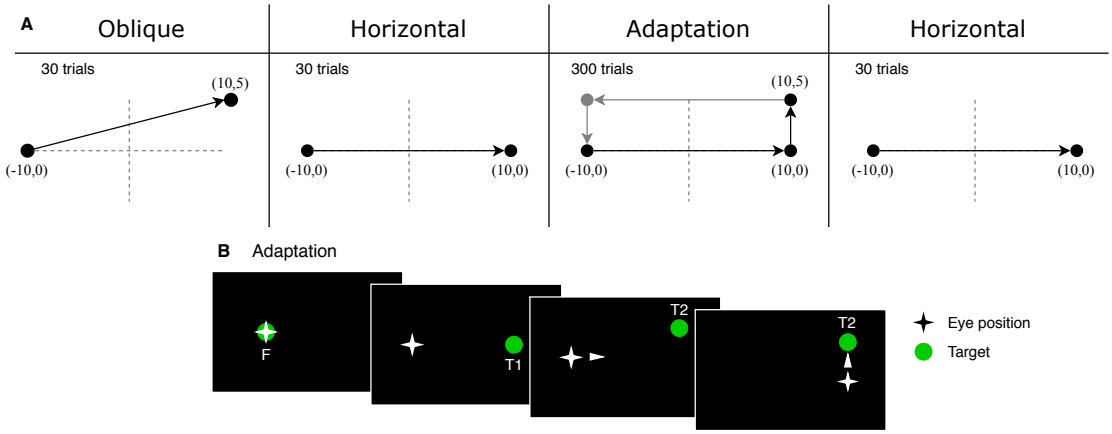


Figure 3.1. Subjects realized a total of 390 saccades. **A**, 3 conditions were investigated during the study, Oblique: where the saccade target is presented at an oblique angle, Horizontal: saccade target presented 20° on the right at the same height than the fixation target and Adaptation: with a counterclockwise target jump. **B**, Adaptation trials started with a fixation target F, a new target, T1, appeared. As soon as the subject initiated his saccade, the target jumped 5° vertically at a new position T2. T2 became the new fixation target for the next trial. The jump direction remained clockwise during all the adaptation blocks.

100°/s. On average 12% of patients' saccades were rejected while only 6% for controls.

To quantify the presence of learning, logarithmic fits were used on several parameters including the maximum vertical velocity and the end point error. The logarithmic functions were fitted as a function of the trial number. If the 99% confidence interval for the parameter responsible for the curvature did not included 0, the fit was considered significant ($p < 0.01$).

Mixed models were used to compare results of the two groups. These models comported a random effect for each subject, to account for idiosyncrasy, and as fixed effects, took into account,a second intercept for the model residuals, the group and the trial number, and the interaction between them. These model will allow us to test if there are any differences between the two groups, if the behavior change with time, and if this evolution in time differs between the two groups [38].

A moving average with a constant bin width of 3 trials is used to show the effects of learning (fig. 3.4, 3.6). Two-sample t-tests were used to compare the duration of saccades for the two groups during the horizontal and oblique trials. To assess the amount of adaptation, the end point error and the peak vertical velocity were compared between the horizontal trials and the last 30 trials of the adapta-

tion block. Spearman's correlation was used for comparing the FTM-TRS scores with the other parameters, including standard deviation of peak vertical velocity timing.

3.2 Results

We will first focus on the oblique and horizontal saccade trials. In the second part of this section, we will compare the performance of the two groups during the adaptation trials.

The neurological assessment allowed us to obtain the average FTM-TRS score of the two groups: 22/56 for the patient group and 2/56 for the control group.

3.2.1 Oblique and horizontal trials

During the two first blocks of the experiment, participants had to perform saccades between two fixed targets. No significant differences were observed between the control group and the ET patients group during oblique and horizontal trials. For the oblique trials, the X and Y components of the saccades are similar for both groups (first row, fig. 3.2). No differences are observed when comparing the velocity profiles (second row, fig. 3.2). Similar results, not included here, were observed for the horizontal trials. Mean saccade duration of the control group and the ET group was similar, and was in average 75 ms ($t_{(16)} = -0.48, p = 0.63$).

3.2.2 Adaptation trials

At the beginning of the adaptation trials, participants did not expect the vertical jump of the target. In previous studies, healthy participants showed an adaptation of their motor commands by adding a vertical component to their horizontal initial saccade and generating curved saccades towards the final position of the target [34, 37]. Saccades of representative individuals are depicted on figure 3.3a.

Velocity profiles

When looking at the velocity profiles (fig. 3.3b), a decrease in peak horizontal velocity is observed for both groups. This decrease corresponds to a normal fatigue-

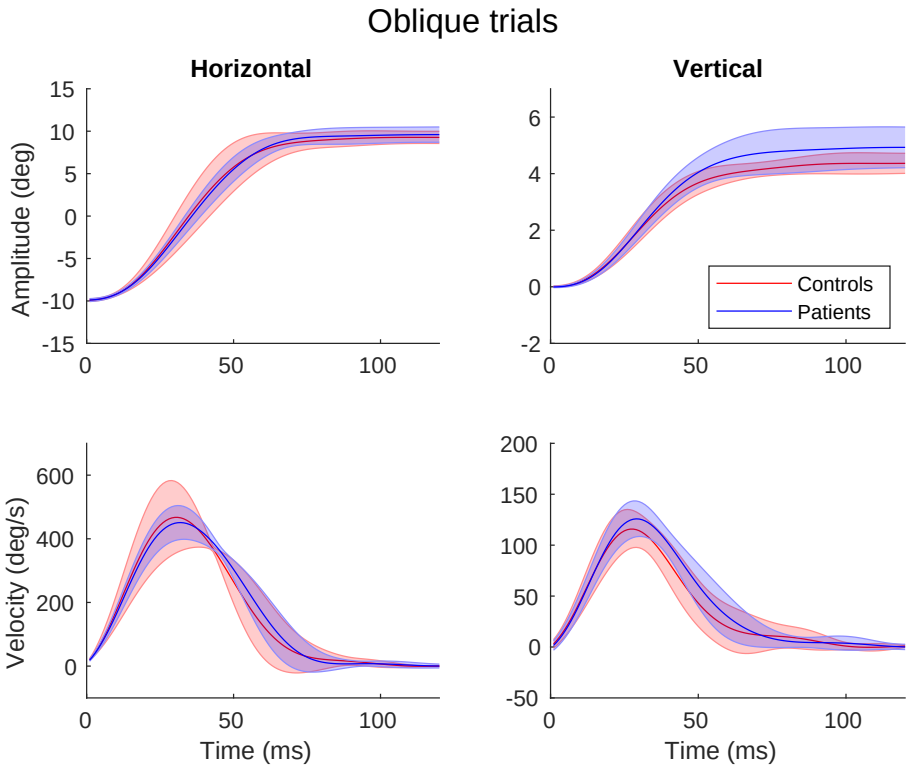
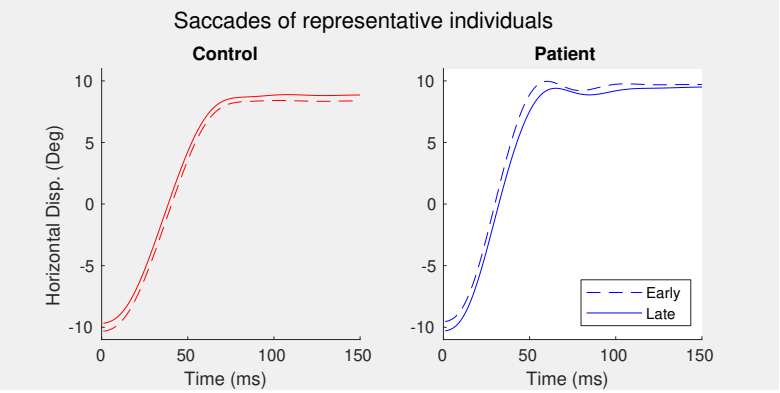
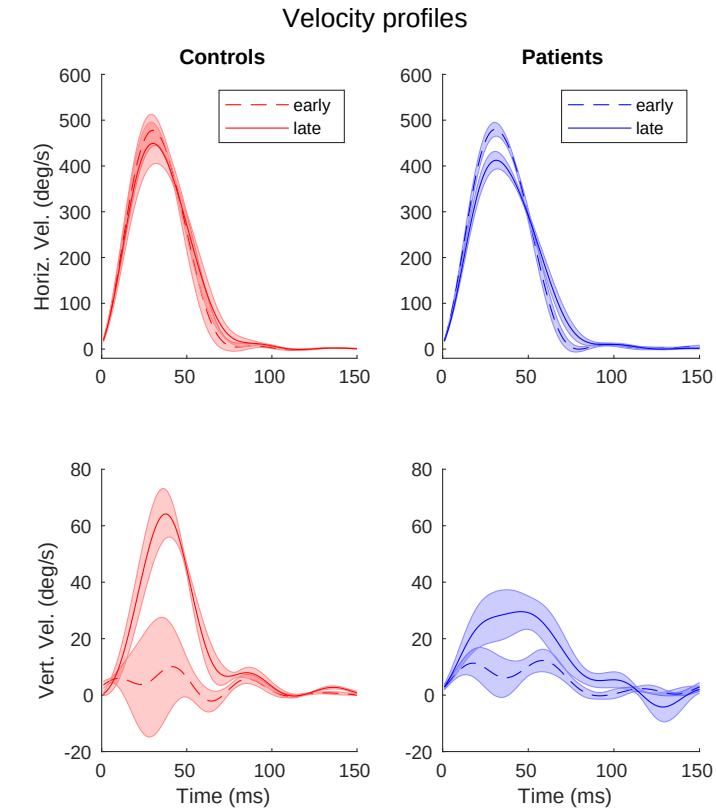


Figure 3.2. Participants behavior during oblique trials, averaged on all the trials of the set. The first row represents the amplitude of the saccade, in the horizontal and vertical directions, second row represents the velocity in both directions. No differences are observed between the two groups during these trials. Error bars represent the standard error of the mean (SEM).



(a) Horizontal component of the saccades of two representative subjects. Averaged on the 10 first (dashed lines) and last (solid lines) saccades of the adaptation trials.



(b) Velocity profiles of the 10 first (dashed lines) and last (solid lines) saccades of the adaptation trials. No differences are observed between the two groups for the horizontal component of the velocity. Peak vertical velocity, at the end of the adaptation block, is smaller for patients. Error bars represent the SEM.

Figure 3.3. Comparison of patients and controls behavior during adaptation trials

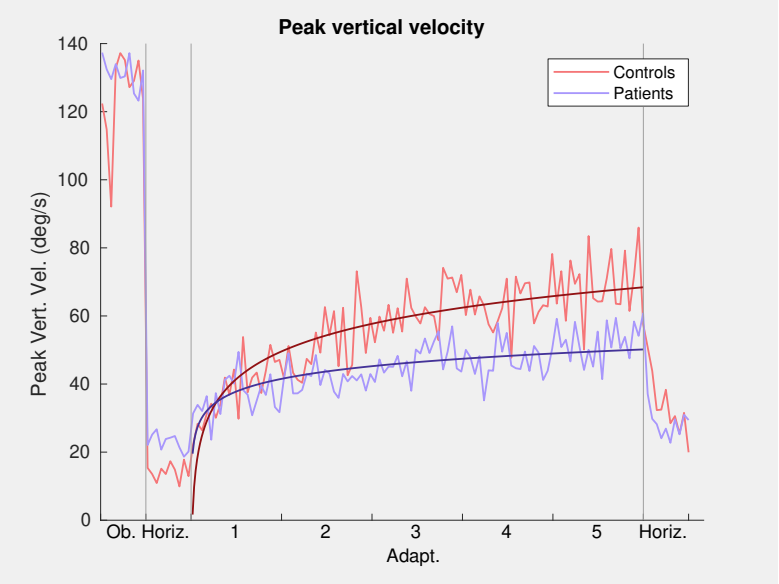


Figure 3.4. ET Patients are impaired in adapting to target jumps but nevertheless show significant adaptation. Peak vertical velocity across the trials is depicted in red for controls and blue for ET patients, gray lines indicate a change in trial type. Each adaptation block contains 60 trials. Fits are significant ($p < 0.01$)

like process, previously reported by similar studies, this decrease is also observed without target jumps [37]. No significant differences were found between controls and patients in horizontal velocity profiles.

Regarding the vertical component of the saccade (second row, fig. 3.3b), at the beginning of the adaptation trials, saccades are mostly horizontal, therefore the vertical velocity is around zero (dashed traces). During adaptation, motor commands adjust and the vertical velocity increases. Saccades will end closer to the final target to reduce the intensity of the corrective saccades. The mean late adaptation vertical velocity profiles of patients and controls show differences (solid traces). The peak vertical velocity and the timing at which this peak occurs are different. We focused on this component for the following analysis.

Peak vertical velocity

As adaptation progresses, the peak vertical velocity should increase. Consequently, saccades should end closer to the last position of the target. The peak vertical velocity across all trials for controls and for patients is depicted in fig 3.4. There is a significant difference in peak vertical velocity between the beginning and the end of the adaptation blocks for both groups (controls: $t_{(6)} = -6.85, p < 10^{-3}$, patients: $t_{(26)} = -4.46, p < 10^{-3}$).

Due to the considerable difference of sample size between the two groups, the hypothesis that the peak vertical velocity at the end of the adaptation block is

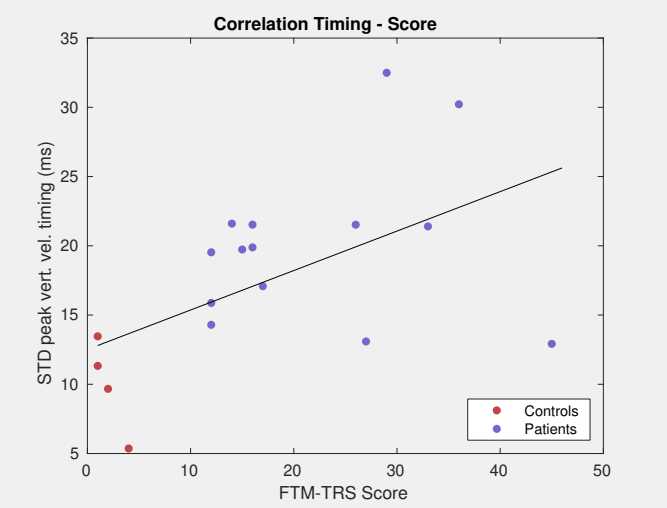


Figure 3.5. Standard deviation of timing at which occurs the peak vertical velocity over the last 30 adaptation trials. Correlation with the FTM-TRS score = 0.54, linear fit = $p < 0.01$.

equal in both groups can not be rejected with the help of t-tests ($t_{(16)} = -0.84, p = 0.41$).

However, mixed models analysis revealed a significant effect of the trial number ($t_{(4868)} = 7.32, p < 10^{-4}$), and the interaction of the group and the trial number ($t_{(4868)} = -4.83, p < 10^{-4}$). These models took into account, an intercept for each subject and for the residuals. And studied the effect of the group (patients or controls), the trial number and the learning rate (interaction of group and trial number) on the peak vertical velocity. This supports that the two learning curves depicted in fig. 3.4 are indeed different.

The timing at which this peak vertical velocity was observed was on average the same for both groups, 40ms after the initiation of the saccade. No significant difference was found at the end of the adaptation ($t_{(16)} = -1.1, p = 0.31$).

However, ET patients' behavior was more erratic in comparison with the control group. The standard deviation of the peak velocity timing at the end of the adaptation trials was higher for ET patients than for controls ($t_{(16)} = -3.27, p < 0.005$). With an average STD of 19 ms for the patient group and only 10ms for the control group. This standard deviation is correlated (0.54) with the FTM-TRS score, see fig 3.5. A standard least-square linear regression highlighted a clear dependency of the tremor score for this variable ($p < 0.01$).

Vertical endpoint

Another marker of adaption is the end point of the primary saccade. The jump of the target induces an end-point error that needs to be corrected by a second

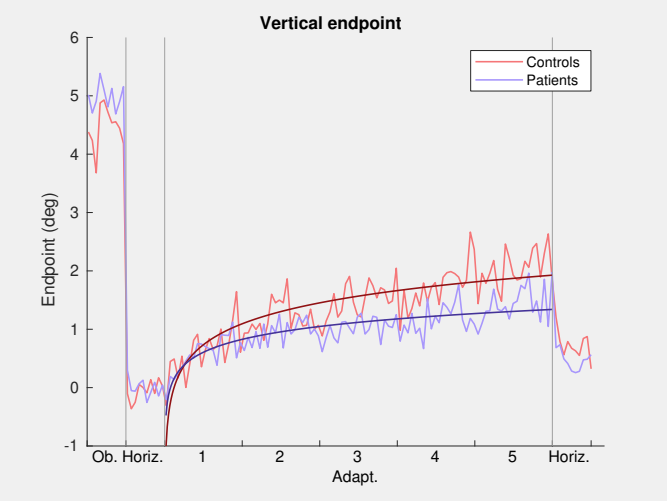


Figure 3.6. Vertical end point across the trials in red for controls and blue for ET patients, gray lines indicate a change in trial type. Each adaptation block contains 60 trials. Fits are significant ($p < 0.01$)

saccade. In response to this error, the subjects will learn to produce saccades that finish closer and closer to the second target in order to reduce the magnitude of the corrective saccade. Significant differences in vertical end point were observed in the two groups between the horizontal trials and the end of the adaptation block (controls: $t_{(6)} = -7.36, p < 10^{-4}$, patients: $t_{(26)} = 5.18, p < 10^{-5}$)

Indeed, between the horizontal trials and the end of the last adaptation block, an averaged increase of 2.14 degrees is observed for control subjects and only 1.6 degrees for the ET group.

Mixed model analysis also confirmed significant differences ($t_{(4868)} = 7.51, p < 10^{-4}$) of the learning curves between patients and controls and revealed a significant effect of the trial number ($t_{(4868)} = -4.13, p < 10^{-4}$).

After each break, subjects exhibited a strong decrease in end-point vertical error, a rapid forgetting that is often attributed to the different timescales of motor adaptation, see section 2.3. This reduction recovers quickly after a couple of trials. No significant differences were observed in the magnitude of this drop, with respect to the last bin of each set ($t_{(16)} = -0.27, p = 0.79$).

Chapter 4

Upperlimb adaptation

This task is inspired by the work of Smith and colleagues [33]. Subjects performed movements towards a series of targets while holding the handle of a robotic device. On some trials the robot applied forces to the hand to perturb the movement. Perturbations produced large errors in the subjects' trajectories, thereby inducing an adaptation of participants' movements to the error. The position of the handle and the force applied on it by the subject were recorded. We used two different quantification of adaptation. Firstly, adaptation was measured as a reduction of the aiming error over trials and, secondly, as an increase in correlation between the force applied by the participant and the force applied by the robot (environmental force).

4.1 Method

Experimental set up and design During this experiment, subjects performed movements in a perturbed environment. The perturbations were applied with a robotic device, the KINARM endpoint robot. Participants held the handle of the robotic device, on which motors can apply forces deviating subjects' movements. Subjects did not have direct vision of their hand, instead they were looking at a screen on which visual targets were projected, among them a cursor representing their hand position. During the experiment, three targets were displayed in addition to the hand cursor: a start target inside which the participants had to place the hand cursor to initiate their movement and two goal targets, all spaced 10cm apart. For each trial, one of the two goal targets was selected randomly to perform the movement. The experimental set up is illustrated in fig 4.1a.

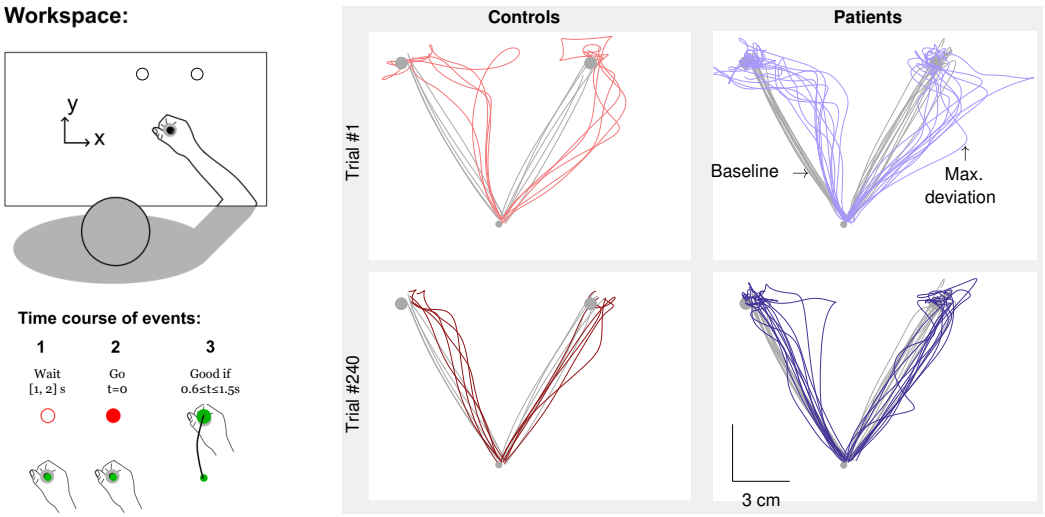


Figure 4.1. A, Illustration of the workspace, participants reached the targets while holding the handle of the device. Movement onset was cued by a change of target color. Adapted from [26] **B,** Traces of every subject during the first (first row) and last (second row) trial of the adaptation block, in both directions. Grey traces corresponds to the last trials towards each target during the baseline trials.

The device recorded the force applied on the handle and the hand position. These recordings are important to define the perturbation. Subjects performed their movements in a clockwise curl force field. In this field forces are perpendicular to the subjects' hand velocity. The forces applied by the robots are determined by the following equation:

$$\begin{bmatrix} F_x \\ F_y \end{bmatrix} = \begin{bmatrix} 0 & 15 \\ -15 & 0 \end{bmatrix} \begin{bmatrix} V_x \\ V_y \end{bmatrix} \tag{4.1}$$

The experiment was divided into 5 sets. One trial corresponded to one movement towards a target. Participants started with a set of 40 baseline trials, without any perturbation, with 20 movements towards each goal target. The experiment continued with 4 sets of 66 movements, made up of 30 trials with the force field turned on and 3 catch trials, in which the perturbation was removed, in both directions. The order in which the trials ware presented was randomly selected by the KINARM software, and the catch trials were unpredictable.

Participants were instructed to perform their movement within 600ms to 1500ms, including reaction time. Movement onset was cued by a change of target color. Movement was successful when subjects were able to stop inside the target within the specified time window. For each successful movement, a score shown on the screen was incremented. This score and the feedback about the movement timing was presented to encourage participants to perform uniform movements, but all trials were kept for analysis.

Subjects A total of 17 patients registered for the study, but only 12 of them were included in the final analysis (eight female and four male, mean age 57 year, range 28—86). The group kept for both analyses is not the same. For the most severely impacted patient, maintaining the hand in the start target was impossible and therefore the experiment could not be performed. Two patients were excluded due to some doubts about the ET diagnostic, another dropped out during the experiment and finally a last patient was excluded from the analysis due to a success rate bellow 50 %. A discussion on this point can be found in section 5. The FTM-TRS score was computed the same way as previous experiment.

Due to the lock-down in consequence of the COVID-19 pandemic, we only recruited a small control group. It is constituted of 5 subjects (4 female, 1 male, mean age 57 years, range 27—74).

Data analysis The position and force recorded were sampled at 1000Hz and digitally lowpass filtered using a 3 order dual-pass butterworth filter (cutoff frequency 10Hz).

Start and end of the movements were detected when the tangential hand velocity exceeded or fell below a 0.03m/s speed threshold for at least 200ms.

To assess adaptation, we investigated several parameters, including path length, movement duration, maximum deviation (defined as the maximum perpendicular distance between the hand trajectory and a straight line connecting start and end target: see fig 4.1a), lateral and forward velocity.

We also focused on two parameters, the aiming error and the correlation between the force applied by the subject and the environmental force. Based on the rationale that the angle extracted at the beginning of the trajectory reflected anticipation for the force field whereas the correlation calculated over the whole trajectory included anticipatory and feedback control components.

The aiming error was defined as the angle between the subject's trajectory at 300ms and the target direction.

Different forces are acting on the handle, the force of the robot due to inertia and friction, F_r, the environment force, commanded by the robot, F_{env}, and the force at the interface of the hand and the handle, F_h, measured by the force transducers. The handle acceleration is proportional the force acting on it

$$m\ddot{x} = F_r + F_{env} + F_h$$

The Pearson's correlation between environment force and measured force is a good marker of adaptation. Indeed, the commanded force is computed based on the forward velocity and a scaling factor. The difference between this commanded force and the measured force is well correlated with the lateral acceleration of the handle. An error remains because the forces linked to the dynamics of the robot, F_r and sampling inaccuracies are neglected. However, these factors do not significantly influence the correlation. Indeed, F_r and F_{env} remain nearly constant during all the trials due to the constraints imposed on movement duration. Therefore, if there is a change observed in the correlation between the environmental and the measured force during the trials, it must be due to a change in control, F_h. An increase in correlation reflects a better adaptation to the force field.

Logarithmic functions were fitted to the learning curves, the curves representing the typical evolution of markers of the adaptation (fig 4.5a and 4.6), those fits were regarded as significant when the 99% confidence interval of the parameter responsible for the curvature did not include zero (corresponding to a p-value of $p < 0.01$).

Mixed models were used to compare results of patients and controls. An intercept was included for each subject and for the residuals, while group, trial number

and interactions between group and trial number were taken into account as fixed effects. [38]

4.2 Results

We will first compare the results during baseline trials, and continue with the results of the adaptation trials.

The neurological assessment revealed an averaged tremor score of 20/56 for the patient group and 2/56 for the control group. The tremor score of one control subject is missing, however, it will be added to the database as soon as possible.

4.2.1 Baseline trials

The experiment started with 40 trials, 20 movements towards each target. During these trials the force field was turned off, allowing the subjects to get familiar with the task, and providing us a way to compare the movements of the two groups when no perturbation was encountered. The last trial of this set in both directions and for each subject is depicted in gray in figure 4.1b.

A few metrics can be used to characterize and compare movements, including path length, movement duration and maximum trajectory deviation (see fig. 4.2a). At the end of the baseline trials, considering the last 10 trials, no significant differences were observed in any of those parameters between the control and the patient group (path length: $t_{(15)} = -1.92, p = 0.07$, movement duration: $t_{(15)} = 0.09, p = 0.93$ and deviation: $t_{(15)} = -0.35, p = 0.73$). This task was not designed to observe the patients' tremor, but especially to study their abilities to adapt and respond to a perturbed environment. As visible from the baseline traces (fig4.1b), the movements patients are performing when the field is turned off combined with the experimental set up are not enough to trigger a tremor. The movements of the two groups can therefore be compared without any interference from eventual oscillations.

No difference of reaction time between the two groups was observed ($t_{(15)} = -0.58, p = 0.56$).

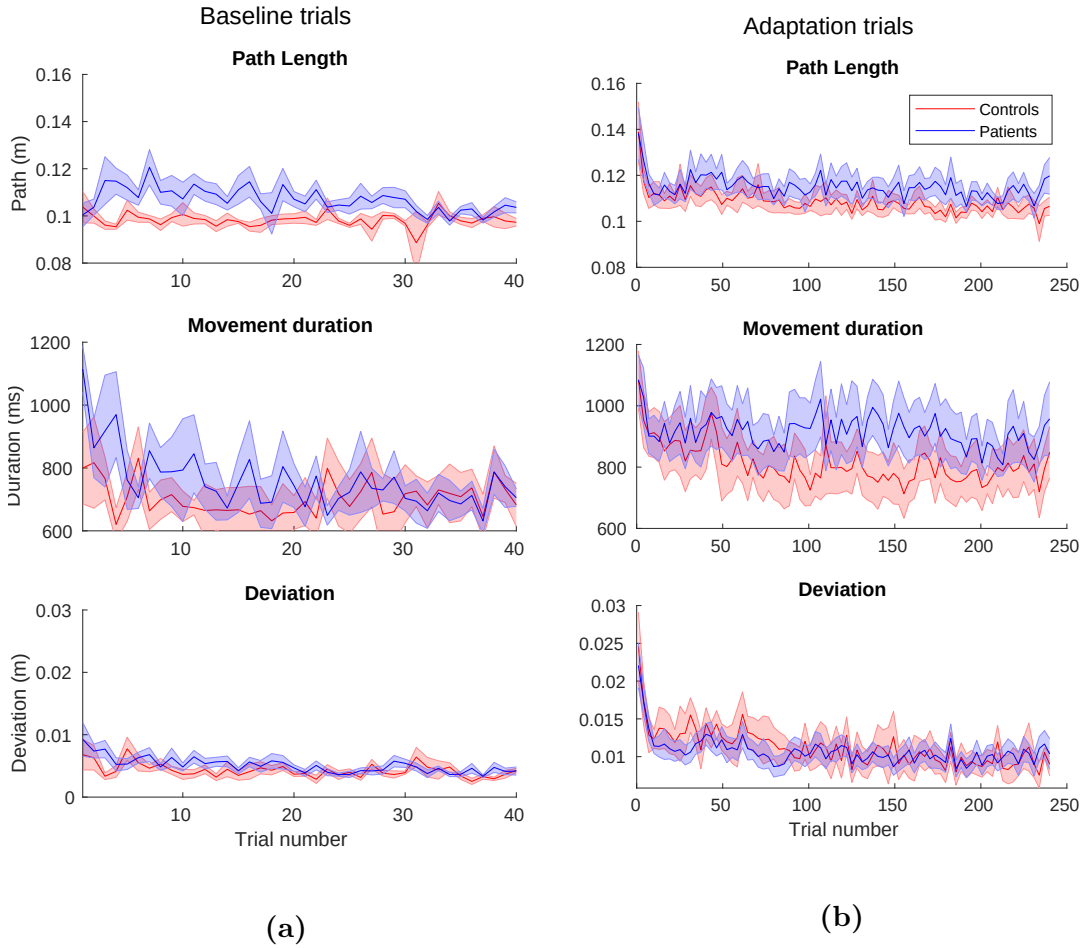


Figure 4.2. Evolution of the path length, movement duration and maximum trajectory deviation during the baseline trials **(a)** and the adaptation trials **(b)**. Shaded areas correspond to standard error of the mean (SEM).

4.2.2 Adaptation trials

First movements in the field are heavily impacted and exhibit large errors (first row, fig 4.1b). To reach the final target within the good time limit, participants have to respond with large corrective movements. With training, subjects learns to compensate for the perturbation, their movements are adapted to return as close as possible to the optimal path, the straight line, and the error is reduced. After the 240 adaptation trials, the movements are closer to baseline performances (second row, fig 4.1b).

Global trends

To compare patients' and controls' movements, we focused on the same parameters as during the baseline trials. They are summarized in figure 4.2b.

We cannot reject, with t-tests, the null hypothesis that the means are equals for both groups (path length: $t_{(15)} = -1.61, p = 0.13$, movement duration: $t_{(15)} = -0.97, p = 0.35$ and deviation: $t_{(15)} = -0.66, p = 0.52$). Fitting mixed models over the two groups data showed only significant effects of the trial number, validating a change in the studied parameters between early and late adaptation, and no significant effect on the group or the interaction between the group and the trial number, implying that the two groups behavior and their learning rate are not statistically distinguishable. Note: A modest ($value < 10^{-5}$) but significant effect of the interaction between the group and the trial was found for the deviation. Results are available in table 4.1. More controls are needed to confirm this trend. The reaction time did not differ between the two groups ($t_{(15)} = -0.97, p = 0.34$).

Lateral velocity

The velocities can be divided into forward velocity, in the direction of the target, and lateral velocity, perpendicular to the target direction. Ideally, perpendicular velocity should be zero as any lateral velocity implies a deviation of the hand from the straight line and only lengthen the path and increase the cost of motor command. The last movement in the baseline block is nearly following a straight line for both groups (see fig 4.3, first row).

When the force field is introduced, the hand is deviated from its optimal trajectory. This deviation can be seen in the lateral velocity profiles (fig 4.3, second row). We can see an adaptation of both groups as the lateral velocity decreases with

	Trial	Group	Group:Trial
Path Length	$t_{(3802)} = -3.5$, $p < 10^{-3}$	$t_{(15)} = 1.17$, $p = 0.26$	$t_{(3802)} = 0.64$, $p = 0.52$
Movement Duration	$t_{(3802)} = -3.74$, $p < 10^{-3}$	$t_{(15)} = 0.93$, $p = 0.37$	$t_{(3802)} = 1.05$, $p = 0.29$
Deviation	$t_{(3802)} = -8.26$, $p < 10^{-4}$	$t_{(15)} = -1.5$, $p = 0.15$	$t_{(3802)} = 4.56$, $p < 10^{-4}$

Table 4.1. Results of the mixed model analysis for the adaptation trials. Trial represents the interaction of the trial number on the studied parameter and therefore its evolution across the trials, Group captures the differences between the two groups and Group:Trial captures the interaction between the group and the trial number, and therefore the differences of evolution across the trial per group, useful to compare the evolution of the two curves.

learning. The performances on the last trial considerably improved and more closely resemble the behavior in the baseline condition. In figure 4.3 trajectories for patients were cut after 1500ms. Many patients continued to oscillate for more than 2500ms following the end of the movement, a behavior that remained present despite many adaptation trials.

Correlation between measured and environmental forces

One measure of the adaptation is the correlation between the environmental force and the force applied by the subject on the handle. The field force is directly linked to the subject's hand velocity, see eq. 4.1. Figure 4.4a illustrates the lateral forces applied by the subject (solid lines) and the environment forces (dashed lines). A net improvement can be observed between the first and the last trial. Subjects appear to have a better control of their movements, stopping more easily and returning to a bell shaped curve (smoother movements) and without the corrective movements that can be observed during the first trial. It is interesting to note that even if some patients might have difficulties to stabilize their hand in the target and oscillates, most of the force needed to get to the final point is applied at the beginning of the movement, within the same time frame as controls.

Since the perturbation experienced in each trial depends on the subjects' hand velocity, it is important to ensure that movement are similar and can be compared. The analysis of the peak forward velocity, did not reveal any significant differences over the end of the adaptation block ($t_{(15)} = -0.2, p = 0.84$), see fig 4.4b. The timing at which this peak occurs is similar for both groups ($t_{(15)}$=$-0.05, p$=0.96).

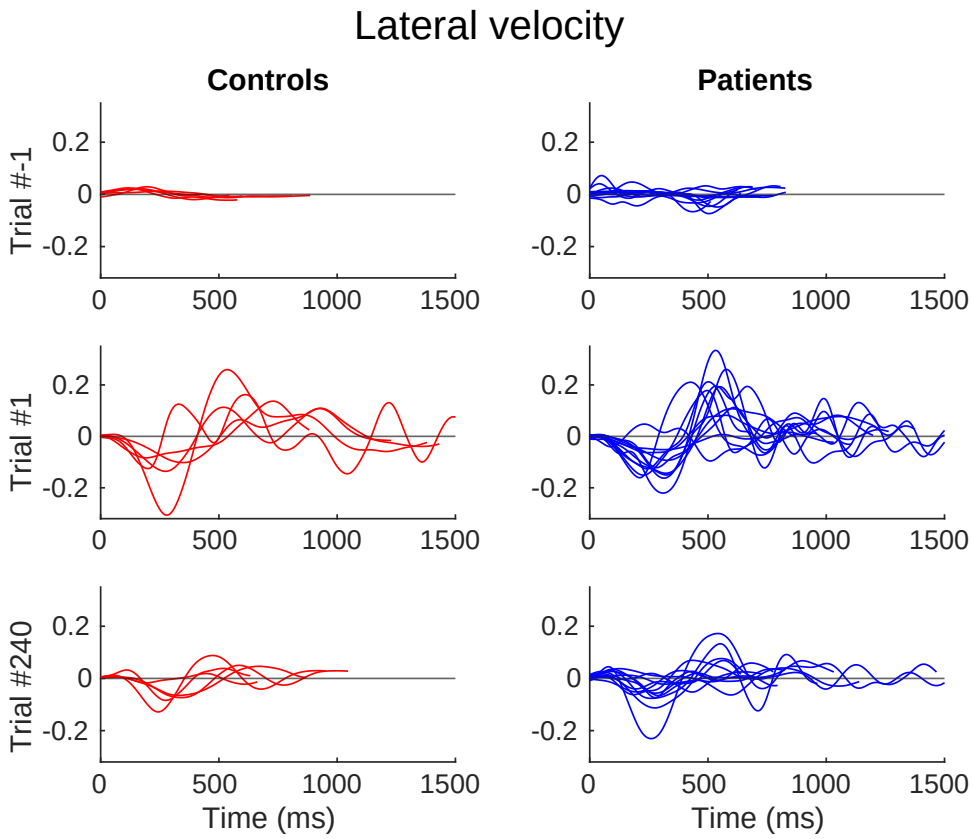
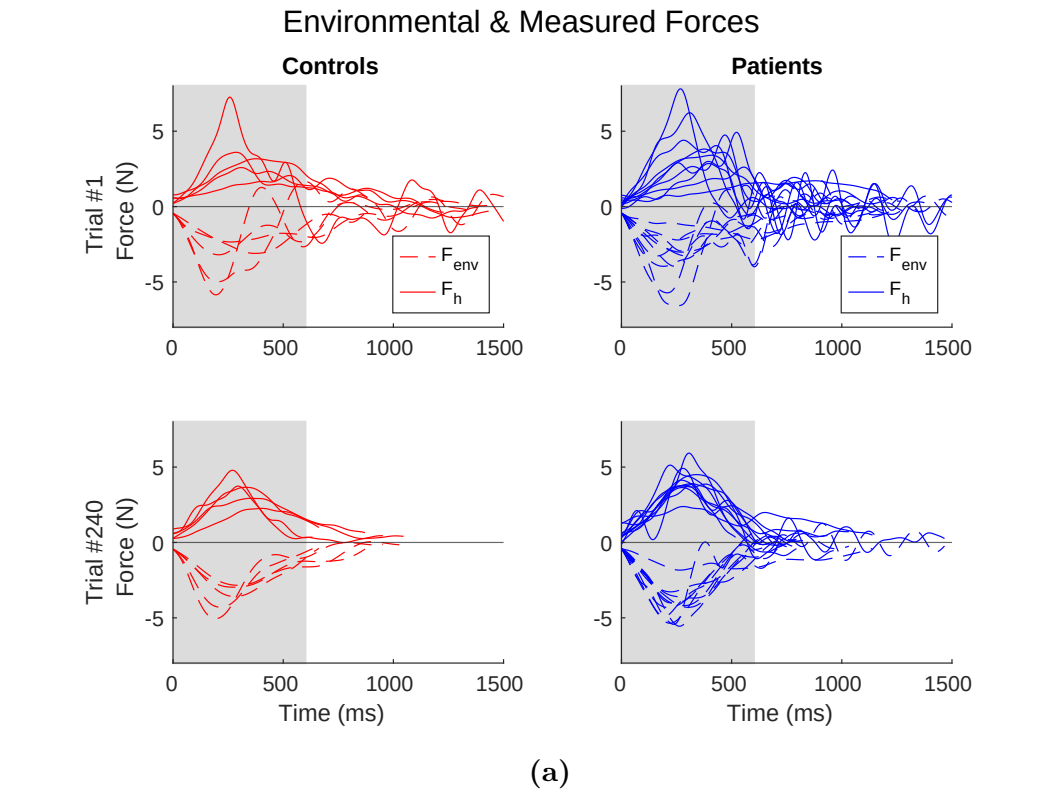
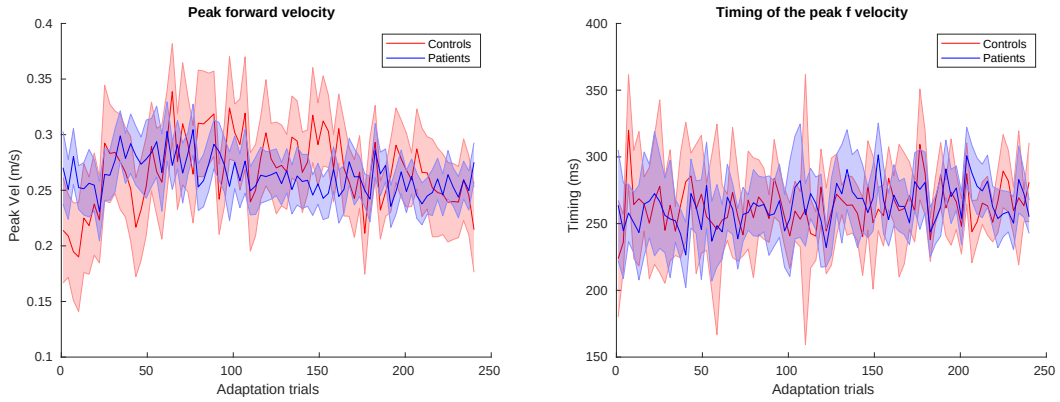


Figure 4.3. Lateral velocity for all the subjects during: the last trial of the baseline block, the first and the last trials of the adaptation block. Subjects adapted their movements to the force field and reduced the lateral velocity with learning. Movements for patients were cut at 1500ms, but many patients continued to oscillate for more than 2500ms following the end of the movement.

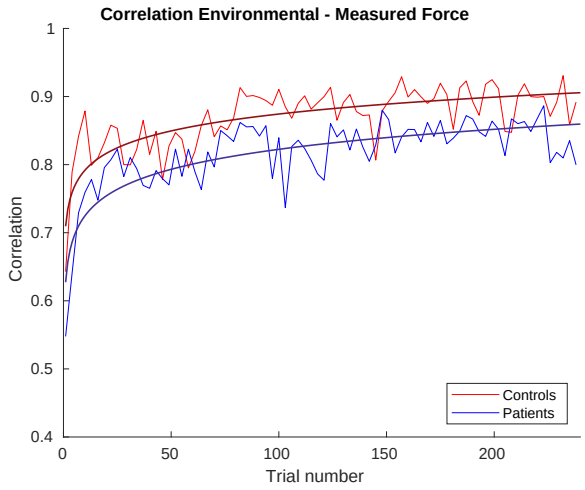


(a)

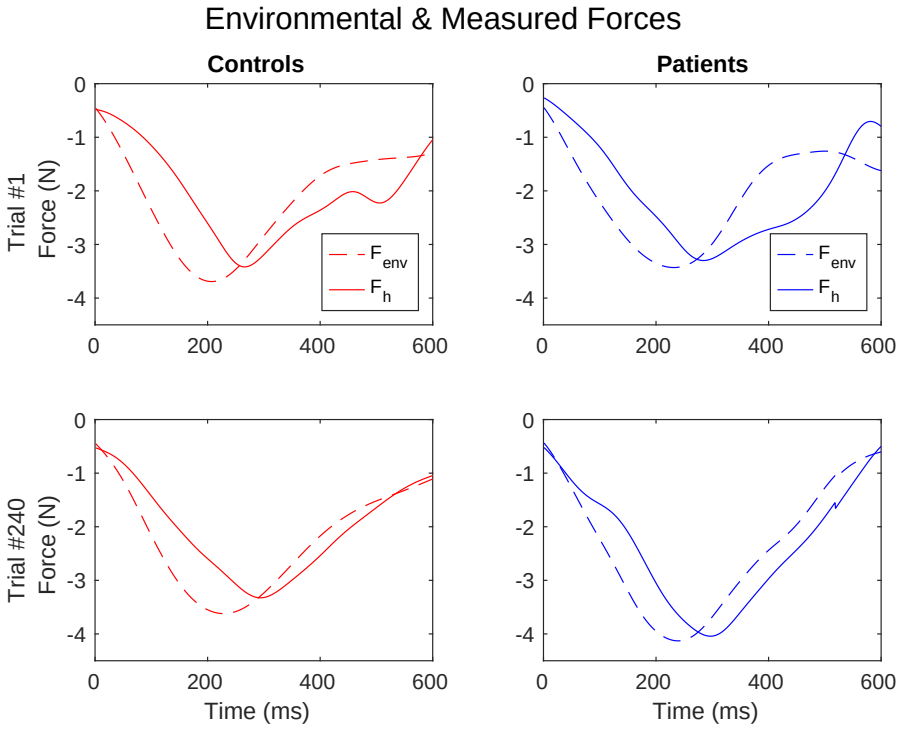


(b) (c)

Figure 4.4. **A** Lateral forces for each subject, during the first and last trial of the adaptation set. Dashed lines: Forces applied by the robot, F_{env}. Solid lines: Forces applied by the participant on the handle, F_h. Correlation is computed over the shaded area. **B** Peak forward velocity across the adaptation trials. **C** Timing of the peak forward velocity across force field trials. **B&C** No significant differences were observed between the two groups. Error bars represent the SEM.



(a)



(b)

Figure 4.5. **A** Evolution of the correlation across the force field trials. Both groups adapted to the perturbation, however, patients' adaptation remained smaller. Logarithmic fits are both significant $p < 0.01$. **B** Mean force traces, with appropriate signs, over the correlation window. The traces became very similar, which increases the correlation between them.

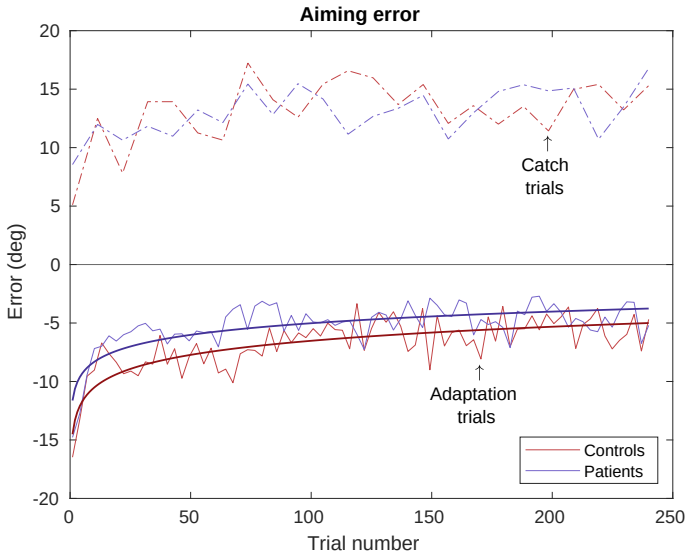


Figure 4.6. Aiming error at 300ms across the trials. Dashed lines represents the aiming error during the catch trials. Both groups anticipated the force field after a few trials. This anticipation increased with time, which reduced the error during the force field trials, and increased the error of the catch trials. Logarithmic fits are significant $p < 0.01$

The correlation between the two forces can be seen in figure 4.5a. This correlation was computed over the first 600ms of the movement, corresponding to the shaded areas in figure 4.4a. The correlation increases with time as subjects are adapting their motor commands to the perturbation field. However, the patients' correlation curve remained lower. Mixed model analysis showed that there was an effect of the trial number ($t_{3801} = 3.29, p < 10^{-3}$), and an effect of the group ($t_{15} = -2.48, p < 0.05$) but no effect of the interaction between the group and the trial ($t_{3801} = 0.76, p = 0.44$). Patients appear to adapt less to the task, but the rate at which their performance improves over the trials was similar to controls.

Aiming error

The aiming error, depicted on fig. 4.6, measures the error between the trajectory and the optimal path 300ms after the beginning of the movement. The error measured during the catch trials reflects the force applied by the participant in anticipation of the force field. Fitting mixed models to the data showed a significant effect of trial number ($t_{(3788)} = 5.2, p < 10^{-4}$) and a small but significant interaction between the trial number and the group ($t_{(3788)} = -2.14, p < 0.05$). However, no significant influence of the group was found ($t_{(15)} = 1.85, p = 0.08$). Continuing the experiment with more controls is needed to confirm or refute these findings.

Chapter 5

Discussion

Is motor adaptation impacted in Essential Tremor? The two experiments conducted allowed us to shed some light on this question. We know that the cerebellum plays a major role in the generation of the tremor [12], and we also know that several mechanisms including motor adaptation rely on the integrity of the cerebellum [21]. Testing the motor adaptation abilities of ET patients allows us to connect the dots between these two separate findings. The two tasks performed during this study indicate an alteration of patients abilities to adapt their motor commands in response of a perturbed environment. These findings support the implication of the cerebellum in the generation of Essential Tremor.

Main results of the saccadic adaptation task

A saccadic adaptation task is interesting to observe the adaptation between the trials as movements are two quick to integrate the sensory feedback impacted by the delays.

Saccades are usually not impaired in ET. We observed no significant differences between the control and patient groups during baseline trials. These resutls are in line with previous studies [39].

However, differences can be observed when looking at adaptation trials. The vertical velocity component of the saccade, which we used to measure adaptation, was lower for ET patients. The vertical velocity peak follows an expected exponential growth, however, this growth remains significantly inferior compared to controls' behavior. More variability is observed in ET patients adaptive motor commands, especially in the timing of the vertical velocity peak. This variability was correlated with their FTM-TRS score, highlighting an interesting correlation between

a quantitative variable, the motor command variability, and a subjective measure, the tremor score.

The peak velocity is not the only factor affected, the vertical end point, directly linked to the peak vertical velocity, remained lower for ET patients during the whole experiment. While some adaptation was observed in both groups, it was limited for ET patients. These results corroborate the link between cerebellar dysfunction and ET.

Previous research illustrated that a delay mismatch between the true delay inherent in the sensory system and the estimated delay could generate oscillations and difficulties to stabilize the movement. Models of saccadic eye movements exhibited overshoots in eye saccades when the delay was underestimated, see fig. 2.2. [1] Saccades profiles of patients showed qualitative similarities with these results, a behavior that is not present in controls' saccades. More research is needed to quantify this effect, however these results highlight the need to carry on research in that direction.

Some limitations are specific to this design. First, in addition to the eye tracking internal calibration, an additional calibration could be included at the beginning of each block. The experiment lasted approximately 50 minutes and ideally, the subjects should stay still during the whole time. However, the position is not comfortable, and very difficult to maintain for the subjects, despite a good adjustment of the chair height. Between the blocks, subjects needed to take a break from this position. The set-up is designed to limit errors due to this movement, the forehead bar limits the possibilities of different positions and ensure a constant distance between the subject and the screen. Lateral displacement was corrected using the eye position at the beginning of the saccades. Despite the need to improve this aspect of the protocol, the results obtained with controls were similar to results in the literature [34, 37].

A second interesting amelioration would be the inclusion of more saccades after the adaptation block, in order to observe the forgetting process and the time needed to return to baseline behavior.

During this experiment, most of the patients had no or mild head tremor. However, with participants with a strong head tremor, it would be impossible to maintain the recording system still. This could therefore be a limitation in patients participation.

Main results of the upper limbs adaptation task

At the end of baseline, no differences were observed between the two groups, patients and controls completed their movement within the same time frame and followed the same path. No oscillations were observed in patients' trajectories during the baseline condition. The task is not designed to trigger a tremor, with short movements and the handle giving a support to the participants' arm, the behavior from both groups can be compared in the same conditions.

Initially, in the force field, both groups showed strong deviation from their baseline trajectories. Over time, they adapted their motor commands to the force field, and compensated for the perturbation in order to reduce the error. However, this compensation remained inferior for ET patients. The correlation between the force applied by the robot and the force applied by the participant increased, but remained lower for ET patients compared to controls.

A second metric of learning, the aiming error, did not show differences between the two groups. Several studies hypothesized that adaptation mechanisms act on multiple timescales [28–30]. Anticipation mechanisms and online control differ and act over a different time scale. In this case, some mechanisms might be more affected than others, resulting in differences on various learning metrics. Anticipation of the force field could be unaffected while corrective actions initiated during the movement might be impacted by a non-optimal feedback loop. This hypothesis is coherent with the results observed during this experiment. No differences were found when studying the anticipation of the subject with the aiming error. The impact of the sensory feedback on this error is very limited, indeed, the error is computed at 300ms and responses emerging from the feedback loop can be observed at the earliest 200—250ms after movement initiation [30]. While differences were observed when taking into account the whole movement with the correlation. Differences might be caused by a dysfunctional integration of sensory feedback during the movement, possibly a delay mismatch. This may explain why no differences were observed in movement initiation. These results should be taken with a grain of salt but justify the need to continue research in this direction.

In addition to the previous results, some patients, despite their abilities to perform most of their movements in the same timing as controls, showed difficulties to stop in the final target and oscillated for a long time after the end of the trial, up to 3000ms. Difficulties to stabilize using the feedback loop could again be linked to misestimation of the delays, a similar behavior has been observed when modeling a system with a delay mismatch, see figure 2.2. [1]

Unfortunately, our criterion to determine movement onset and offset led to the ex-

clusion of some interesting movements. Specifically, movement end was detected when the speed fell below a 3cm/s threshold for at least 200ms. Movements without a clear end were excluded from the analysis. This resulted in the exclusion of all the trials where patients were unable to stabilize their hand in the final target. These movements will be included in future analysis and might lead to interesting insights. For the controls, it represented in average 1.8 movements over the whole experiment, however for the patients groups, it represented 35 movements excluded in average. However, excluding these trials from the analysis allowed us to compare movements that are similar between the two groups.

For further experiments, it would be interesting to adapt the design of the study to include participants that are unable to stabilize in the first target. In the present task, to start a trial, participants had to maintain their hand inside a small target. A task that was impossible for one of the participants who registered for the study. Allowing small oscillations about the target in the protocol would solve this problem.

Limitations common to both experiments

The first and most evident limitation of our work is the size of the control group. Unfortunately, due to the COVID-19 situation, recruitment was suspended. As soon as we will be allowed to continue the experiment, we will recruit the age-matched control subjects. However, the results obtained with the reduced group of controls are in line with previous findings on similar tasks [26, 33, 34, 37].

Second limitation of this analysis is the evaluation of the severity of the tremor. The Fahn-Tolosa-Marin Tremor Rating Scale, used for this purpose, is a useful tool to verify ET diagnosis, however this scale is not specifically designed for Essential Tremor, and contains a set of criteria less relevant for ET. For example, all tremor assessments in the rating scale are weighted equally. As a consequence different types of tremor, such as tongue or hand tremor, contribute equally to the final score. Hence, the score obtained with this scale is not always a good reflection of the true severity of the symptoms. In addition, the questions on everyday tasks included in the rating scale are highly subjective. The detailed description of the score of each task was not included in patients' questionnaire, for the following assessments, this description will be added to the questionnaire. However, difficulties remains, how should patients answer? Do they consider their abilities in the morning or evening? For patients who do not take their medication every day, should they base their answer on abilities on the days they took the mediation or when the tremor is strongest? To limit the errors and the variability of measures, the tremor evaluation was always performed by the same neurologist.

And the tremor drawing score was always realized under the same conditions. In the present study we chose to focus exclusively on tremor of the upper limbs and the drawing score to assess patients' impairments more closely. Taking into account factors influencing the tremor is a possible improvement of our evaluation. We also listed the medication for each subject, but the broad range of treatment and dosage made it more difficult to use. Accounting for stress level or recent alcohol consumption could further improve the reliability of the tremor evaluation. This would be especially relevant when performing a longitudinal study with re-tests following a few months and years after the original assessment.

Lastly, averaging the participants' behavior can be seen as limitation of this study. Indeed, some heterogeneity was observed within the patients group and averaging their behavior might not reflect the reality of some of them. However, the goal is not to capture individual patient's behavior but to draw a global picture of the disorder.

Future directions

Our results shed new light on Essential Tremor. Motor adaptation - a process known to rely on the integrity of the cerebellum - appears to be impaired in ET patients. This behavioral marker of the disorder is not a direct consequence of the tremor, because no oscillations are observed in baseline trials for both tasks. Impaired motor adaptation might be an additional symptom of the disorder. We hypothesize that a misestimation of feedback delays may lie at the root of this impairment. Theoretical simulations have shown that misestimations of sensory delays cause instability in the system ultimately leading to oscillations and overshoots. These estimations steps are believed to be performed in the cerebellum. A misestimation of the delays induces a nonoptimal integration of the sensory feedback. Motor adapatation depending on this sensory feedback, this might explain patients' impaired ability to adapt to new environmental dynamics.

Clinical scales are inherently subjective and the scores are uninterpretable. The difference between a hand tremor of 1 or 3 is unknown and the limits between the scores boundaries are unclear. In contrast measures of adaptation are reliable and do not depend on the evaluation context. Thus we hope to make a double contribution in the long term: 1- to better understand the neural mechanism associated with sensorimotor control by correlating cerebellar-dependent deficits in motor adaptation with tremor, that is effectively failure to stabilize, and 2- to provide objective assessment for these patients based on behavioral measures.

Adaptation is not the only mechanism depending on the feedback loop. One pos-

sible direction would be to test corrective responses of individuals after a postural perturbation. Such behavior could be tested in our lab with the KINARM device, in which participants would have to return and stabilize in a target as quickly as possible following a perturbation. The results obtained in both experiments encourages us to investigate this aspect of the feedback loop.

Another task involving this loop is occulo-manual tracking. One idea is to study subjects' behavior when tracking their hand or an external target with their eyes. We have already developed a protocol for this task, unfortunately due to difficulties encountered when validating this protocol with some subjects, we decided to focus on motor adaptation in this thesis. However, this will be an interesting challenge to overcome in future experiments.

Finally, establishing a link between the performances of patients on different behavioral tasks, their tremor scores and cerebellar connectivity may reveal further interesting insights into the pathology of Essential Tremor.

Essential tremor and motor adaptation

These results suggest a new behavioral marker of the disorder, in line with an implication of the cerebellum in Essential Tremor and compatible with a generation of oscillation in theory of systems. This marker is a new hope for refining diagnostic methods or rehabilitation techniques but requires further validations in the future.

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Appendices

Fahn-Tolosa-Marin Tremor Rating Scale

1-9 Tremor (rate tremor)

1) At rest (in repose). For head and trunk, when lying down
2) With posture holding
   - UE: arms outstretched, wrists mildly extended, fingers spread apart
   - LE: legs flexed at hips and knees; foot dorsi-flexed
     - tongue: when protruded
     - head and trunk: when sitting or standing
3) with Action(ACT) and Intention(INT):
   - UE: finger to nose and other actions
   - LE: toe to finger in flexed posture

Definitions for 1-9

0 = None
1 = Slight. May be intermittent
2 = Moderate amplitude. May be intermittent
3 = Marked amplitude
4 = Severe amplitude

1. Face tremor ……. REST _____

2. Tongue tremor …….. REST _____

POST _____

3. Voice tremor ……. ACT/INT _____

4. Head tremor ……. REST _____

POST _____

5. Right upper extremity tremor ……. REST _____

POST _____

ACT/INT _____

6. Left upper extremity tremor …….. REST _____

POST _____

ACT/INT _____

7. Trunk tremor …… REST _____

POST _____

8. Right lower extremity tremor …… REST _____

POST _____

ACT/INT _____

Adapted from Fahn-Tolosa-Marin Tremor Rating Scale (2013).
Essential Tremor. Retrieved from https://essentialtremor.org/

9. Left lower extremity tremor …….. REST _____

POST _____

ACT/INT _____

10. Handwriting …….. _____

Have patient write the standard sentence: "This is a sample of my best handwriting", sign his or her name and write the date.
0 = Normal
1 = Mildly abnormal. Slightly untidy, tremulous
2 = Moderately abnormal. Legible, but with considerable tremor.
3 = Marked abnormal. Illegible
4 = Severely abnormal. Unable to keep pencil or pen on paper without holding hand down with other hand.

11-13. Ask the patient to join both points of the various drawings without crossing the lines. Test each hand, beginning with the lesser, without leaning the hand or the arm on the table.

Definitions for 11-13
0 = Normal
1 = Slightly tremulous. May cross lines occasionally.
2 = Moderately tremulous or crosses lines frequently.
3 = Accomplishes the task with great difficulty. Many errors.
4 = Unable to complete drawing.

11. Drawing A

Right _____

Left _____

12. Drawing B Right _____

Left _____

13. Drawing C Right _____

Left _____

14. Pouring Right _____
Use firm plastic cups, about 8 cm tall, filled with water to 1 cm from top. Ask patient to pour water from one cup to another. Test each hand separately. Left _____
0 = Normal
1 = More careful that a person without tremor, but no water is spilled.
2 = Spills a small amount of water (up to 10% of the total amount).
3 = Spills a considerable amount of water (> 10-50%)
4 = Unable to pour water without spilling most of the water.

15. Speaking _____
This includes spastic dysphonia if present
0 = Normal
1 = Mild voice tremulousness when "nervous" only
2 = Mild voice tremor, constant
3 = Moderate voice tremor
4 = Severe voice tremor. Some words difficult to understand.

16. Feeding other than liquids _____
0 = Normal
1 = Mildly normal. Can bring all solids to mouth, spilling only rarely.
2 = Moderately abnormal. Frequent spills of peas and similar foods.
May bring head at least halfway to meet food.
3 = Markedly abnormal. Unable to cut or uses hands to feed.
4 = Severely abnormal. Needs help to feed.

17. Bringing liquids to mouth _____
0 = Normal
1 = Mildly abnormal. Can still use a spoon, but not if it is completely full
2 = Moderately abnormal. Unable to use spoon; uses cup or glass
3 = Markedly abnormal. Can drink from cup or glass, but needs two hands
4 = Severely abnormal. Must use a straw.

18 Hygiene _____
0 = Normal
1 = Mildly abnormal. Able to do everything, but is more careful than the average person
2 = Moderately abnormal. Able to do everything, but with errors;
uses electric razor because of tremor
3 = Markedly abnormal. Unable to do most fine tasks, such as putting on lipstick or shaving
(even with electric razor), unless using two hands.
4 = Severely abnormal. Unable to do any fine-movement tasks.

19. Dressing _____
0 = Normal
1 = Mildly abnormal. Able to do everything, but is more careful than the average person.
2 = Moderately abnormal. Able to do everything, but with errors.
3 = Markedly abnormal. Needs some help with buttoning or other activities, such as tying shoelaces.
4 = Severely abnormal. Requires assistance even for gross motor activities.

20. Writing _____
0 = Normal
1 = Mildly abnormal. Legible. Continues to write letters
2 = Moderately abnormal. Legible, but no longer writes letters.
3 = Markedly abnormal. Illegible
4 = Severely abnormal. Unable to sign checks or other documents requiring a signature.

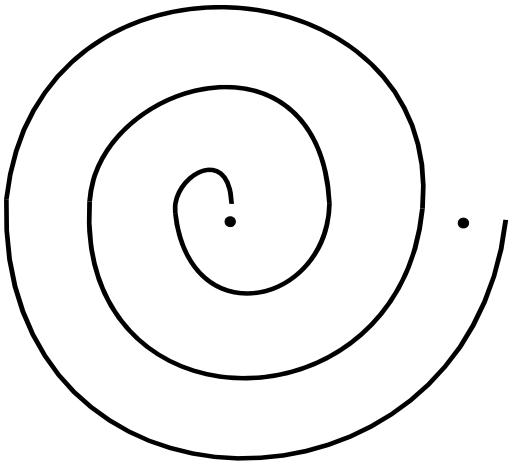
21.Working _____
0 = Tremor does not interfere with job
1 = Able to work, but needs to be more careful than the average person
2 = Able to do everything, but with errors. Poorer than usual performance because of tremor
3 = Unable to do regular job. May have changed to a different job because of tremor.
Tremor limits housework, such as ironing.
4 = Unable to do any outside job; housework is very limited.

Non-Dominant Hand

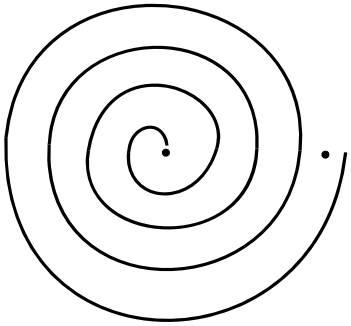
Drawings A, B, and C and make with the _____ Left Hand

_____ Right Hand

DRAWING A



DRAWING B



DRAWING C

Dominant Hand

Handwriting: This is a sample of my best handwriting

_____

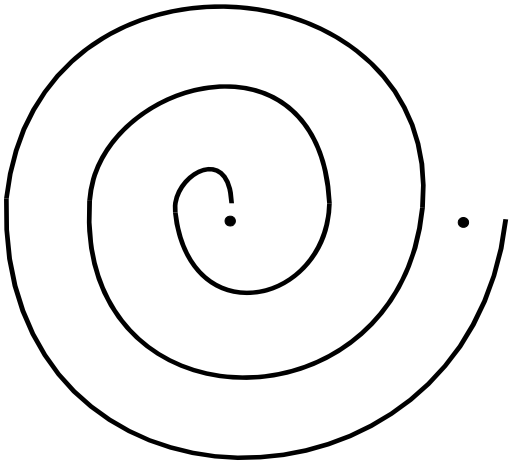
Signature: _____

Date: _____

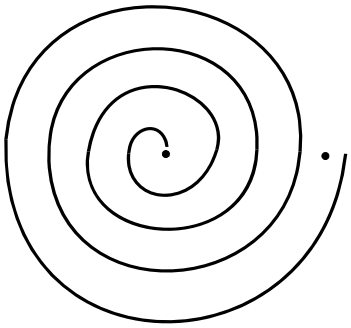
Drawings A, B, and C and make with the _____ Left Hand

_____ Right Hand

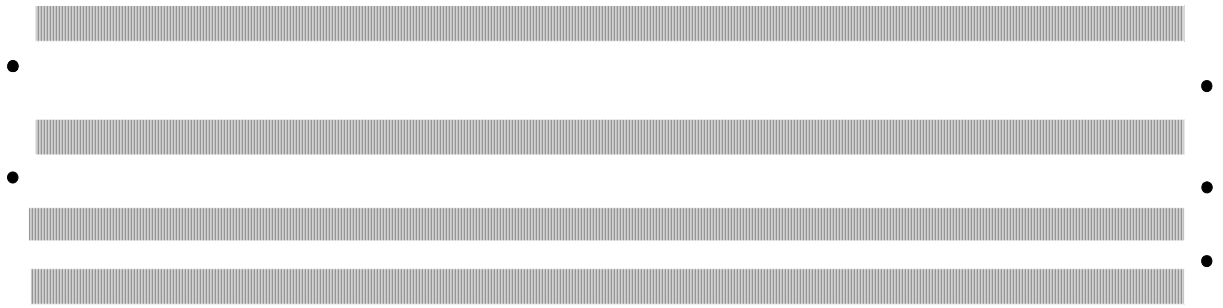
DRAWING A



DRAWING B



DRAWING C



UNIVERSITÉ CATHOLIQUE DE LOUVAIN
École polytechnique de Louvain
Rue Archimède, 1 bte L6.11.01, 1348 Louvain-la-Neuve, Belgique | **www.uclouvain.be/epl**