Adaptability and adaptation to a sensorimotor task : from functional significance of fractal properties to brain networks dynamics

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Adaptability and adaptation to a sensorimotor task: from functional significance of fractal properties to brain networks dynamics

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Sous la direction de Kjerstin TORRE et Stéphane PERREY

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"I am a pretty good learner, but horrible time manager. It's easy to pile on new projects and ideas because we scientists are a curious bunch by nature. There are tons of time management techniques out there, but most of us continue to add items to our own list before we've finished other things. Some of it is the pressure of the academic setting (grants, promotion & tenure, publication, etc.) some of it is the seduction of the intellectual smorgasbord that is science. We can't help it."

Randy McIntosh, Science is hard, December 22, 2017

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Publications arising from this disseration:

1. **Vergotte, G**., Torre, K., Chirumamilla, V. C., Anwar, A. R., Groppa, S., Perrey, S., & Muthuraman, M. (2017). Dynamics of the human brain network revealed by time-frequency effective connectivity in fNIRS. *Biomedical Optics Express*, *8*(11), 5326-5341. https://doi.org/10.1364/BOE.8.005326

2. **Vergotte, G.**, Perrey, S., Muthuraman, M., Janaqi, S., & Torre, K. (2018). Concurrent changes of brain functional connectivity and motor variability when adapting to task constraints. *Frontiers in physiology*. 9, 909. https://doi.org/10.3389/fphys.2018.00909

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2. **Vergotte, G**., Torre, K., & S. Perrey. Adaptabilité ou adaptation ? De la variabilité sensorimotrice aux patterns d'activation corticales. Association Africaine des Sciences du Sport (2A2S), March 17-19th 2016, Hammamet (Tunisia).

3. **Vergotte, G.,** Perrey, S., Muthuraman, M., Janaqi, S., & Torre, K. Sensorimotor adaptation: bridging the gap between brain networks dynamics and behavioral variability, 4th French community for functional Near-Infrared Spectroscopy Conference, October 12-13th 2017, Lille (France).

4. **Vergotte, G**., Torre, K., P. Besson., M. Delorme., & S. Perrey. La spectroscopie proche infra-rouge (Symposium Thématique : Apport de la Neuroimagerie cérébrale dans les Sciences du Mouvement Humain). Association des Chercheurs en Activités Physiques et Sportives (ACAPS), October 29-31th 2017, Dijon (France).

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2. **Vergotte, G.,** Perrey, S., Muthuraman, M., Janaqi, S., & Torre, K. Adaptation in a sensorimotor task: bridging the gap between brain network dynamics and behavioral variability. Workshop Create, August 2017, Montreal (Canada)

Other publications:

1. Besson, P., **Vergotte, G.,** Muthalib, M., & Perrey, S. (2017). Abstract: Test-retest reliability of transcranial direct current stimulation-induced modulation of resting-state sensorimotor cortex oxygenation time course. *Brain Stimulation,* 10(2), 400. http://doi.org/10.1016/j.brs.2017.01.186

2. Delorme, M., Froger, J., Perrey, S., **Vergotte, G.,** & Laffont, I. (2017). Changes in hemodynamic responses during movements of the upper extremities in the acute phase after stroke: A fNIRS study. *Annals of Physical and Rehabilitation Medicine*, *60*, e1. https://doi.org/10.1016/j.rehab.2017.07.016

3. Borot, L., **Vergotte, G.,** & Perrey, S. Different hemodynamic responses of the primary motor cortex accompanying eccentric and concentric movements: A functional NIRS study. *Brain Sciences*, 8(5). https://dx.doi.org/10.3390%2Fbrainsci8050075

Other communications:

1. Delorme. M., **Vergotte. G.,** Perrey. S., Froger. J., & Laffont. I. Changes in hemodynamic responses during movements of the upper extremities in the acute phase after stroke: A fNIRS study. Journée Scientifique Institut Fédératif de Recherche sur le Handicap, September 21th 2017, Montpellier (France).

2. **Vergotte, G.,** Besson, P., Muthalib, M., Torre, K., & Perrey, S. Motor transcranial direct current stimulation (tDCS) effects on directed functional connectivity in the motor network derived from resting state fNIRS, 4th French community for functional Near-Infrared Spectroscopy Conference, October 12-13th 2017, Lille (France).

3. Borot, L., **Vergotte, G.,** & Perrey, S. Hemodynamic response alterations in primary motor area as a function of muscle action: An fNIRS study, 4th French community for functional Near-Infrared Spectroscopy Conference, October 12-13th 2017, Lille (France).

4. Borot, L., Pageaux, B., Laroche, D., **Vergotte, G.,** Lepers, R., Perrey, S. Greater mental demand during eccentric compared to concentric cycling is associated with different prefrontal and parietal cortical responses. Joint Italian-French Workshop on "Cerebral oximetry and functional near infrared spectroscopy (fNIRS)". June 13-15 th 2018, Milan (Italia).

5. Borot, L., **Vergotte, G.,** Pageaux, B., Laroche, D., Lepers, R., Perrey, S. Functional connectivity during eccentric and concentric motor task: different organization of the attentional network. Joint Italian-French Workshop on "Cerebral oximetry and functional near infrared spectroscopy (fNIRS)". June 13-15 th 2018, Milan (Italia).

Contents

Abstract:

The study of fractal properties in biological time series is of increasing interest. Nevertheless, the literature highlights an ambiguity on the causal explanation of the presence of these time series which do not make it possible to distinguish between the effective adaptation made by a subject or his overall adaptability capacities. The aim of this dissertation is to decorrelate these two notions, notably by linking the behavioral level to the cerebral level. Our first study allowed to highlight that the mono-fractal properties could reflect the adaptability of the subjects whereas the multifractal properties would be related to the effective adaptation carried out during the task. The second study showed a correlation between the multifractal properties and the number of brain networks implemented, reflecting the effective adaptation to the experimental constraints imposed. The results of this work have allowed us to better understand the functional meaning of fractal analyzes in terms of effective adaptation and adaptability.

Key words: Adaptation, tapping, fractals, cerebral networks, functional near infrared spectroscopy, dynamical system, connectivity.

Résumé:

L'étude des propriétés fractales des séries biologiques fait l'objet d'un intérêt croissant. Néanmoins, la littérature met en évidence une ambiguïté quant à l'explication causale de la présence de ces séries temporelles ne permettant pas de distinguer entre l'adaptation effective réalisée par un sujet ou ses capacités d'adaptabilité globales. La présente thèse a pour objectif de décorréler ces deux notions, notamment en liant le niveau comportemental au niveau cérébral. Notre première étude a permis de mettre en évidence que les propriétés mono-fractales pourraient refléter l'adaptabilité des sujets tandis que les propriétés multifractales seraient liées à l'adaptation effective réalisée au cours de la tâche. La seconde étude a mis en évidence une corrélation entre les propriétés multifractales et le nombre de réseaux cérébraux mis en œuvre, reflétant l'adaptation effective aux contraintes expérimentales imposées. Les résultats de ces travaux de thèse nous ont permis de mieux comprendre la signification fonctionnelle des analyses fractales en termes d'adaptation effective et d'adaptabilité.

Mots clés : Adaptabilité, adaptation, tapping, fractales, réseaux cérébraux, spectroscopie dans le proche infrarouge, système dynamique, connectivité.

Chapter 1

General Introduction

1.1 A complexity theory approach

"Complexity theory is destined to be the dominant scientific trend on the 1990's"

Lewin, R., 1992. Complexity: Life at the Edge of Chaos (Back Cover).

Complexity considered in a broad sense has common properties whatever the field of application happens to be. In a complex system, the whole is considered as being more – and sometimes less – than the sum of its parts. The system is composed of multiple elements that interact in a non-simple way (Simon, 1991). Imagine or return in a simple way to our first chemistry courses. Although at the bottom of the class the table of Mendeleïev indicates numerous elements, these parts taken individually cannot explain some emergent properties like the di-hydrogen combustion reaction. In the same way, the exchanges between individuals can create in a sense some masterful discoveries like the 2017 Nobel Prize for the discovery of gravitational waves. While this system was generally defined at the edge of the chaos, complex system theory now generally adopts a position between two extremes, not in the extreme at once too chaotic nor conversely too rigid. Whatever the metaphor used, a consensus seems to have developed on the functional organization (or topology) adopted by these systems. For Henry Atlan (1979), the complexity lies in between crystal and smoke in being neither too rigid, nor too "random". On the one hand, crystal is considered to have an organization of its elements that is too rigid between the elements. In this sense, too much disruption of the system can break the crystal. Such a system tends to fall into a too strongly predictable and deterministic way. On the other hand smoke is considered to be a set of totally independent elements (Figure 1A). This organization does not allow creating any kind of structure and therefore remains completely unpredictable. According to Edgard Morin (1994), such types of systems are between order and disorder phenomena. Kauffman (1991) proposes to define a complex system as being between chaos (defined as a complete disorder of the system) and anti-chaos (a strictly rigid organization). Moreover, Paul Valéry considers that "two dangers are constantly threatening the world (complex by definition): order and disorder". This author does not hesitate to add that "between order and disorder reigns a delicious moment". Nevertheless, this positioning between two extremes leads to a dynamic property of complex systems. It does not seem possible to imagine a third "rigid" extreme system situated equidistant from complete order and complete disorder. Complex systems will therefore oscillate between those two phenomena and will involve a dynamics or oscillation between more or less order and more or less disorder.

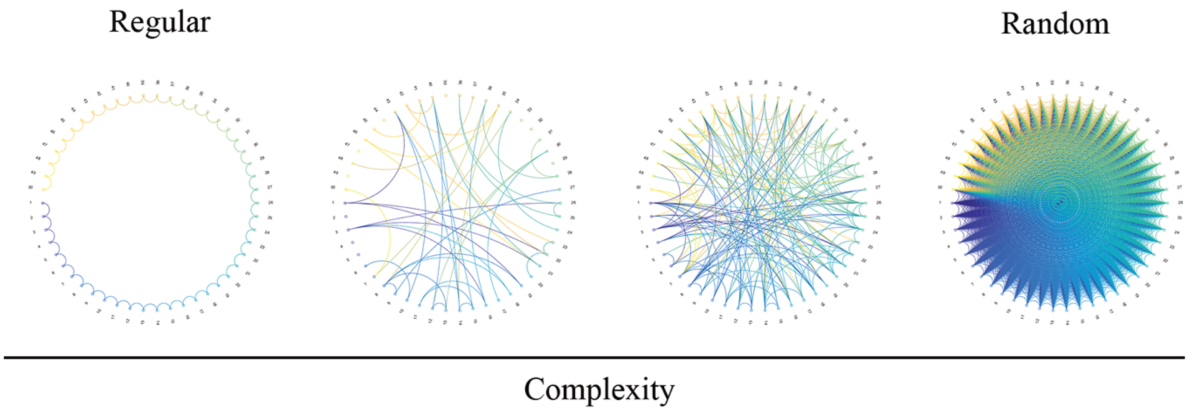

Figure 1A: Effect of topological links modification on the system. On the left: a too rigid system in which all the elements are connected to each other in an identical manner (low cost but low communication between elements). On the middle: two more complex systems comprised between low connections and fully connected network organizations. On the right: a fully connected network where all nodes are connected (high cost). Both, the left and the right system could be eather random or rigid organization.

As the nature of complexity is hard to reveal due to the large number of applications in multiple fields, some researchers proposed to classify the definition (or approach) of complexity in three divisions depending on the discipline/field perspective (Mason, 2001). First, they called “Algorithmic complexity” as a mathematical complexity and a difficulty to describe system characteristics. The drawback of this approach is formulated as algorithmic complexity that “may incorrectly equate data with knowledge”. Lots of real life systems lie beyond algorithmic expressions. Second, they used the term “Deterministic complexity” which originates from the chaos theory. These approaches posit that the system (dynamic per se) can create a stable pattern composed of few elements and can shift (or phase-transit) to another pattern to adapt to external or internal constraints. Nevertheless they considered this approach as a biased concept as it is composed of only two or three variables to explain more complex phenomena. Finally, the third class of complexity was called “Aggregated complexity” and the interest of this approach is based on interactions between multiple elements to create complex behavior. This class gives more importance to the links between the multiple elements that make up the system (dynamic interaction-dominant system) rather than to the number of elements constituting the system (component-dominant system), which would reflect a complicated but not complex system. Combining these second (deterministic) and third (aggregated) definitions fits well with the theoretical approach previously proposed

by Morin and others and studies in the field of human movement science. Complexity (or complex systems) is generally defined only in opposition to simplicity and/or predictability (Morin, 1994). In our everyday life and current language, complexity is understood as complication. Complication refers to the idea that the system is composed of a huge number of components. Interactions between components are generally considered to be of second order and therefore of less importance (if not ignored). The first main point of this dissertation is therefore to adopt an approach that take into account the links between elements which will prove to be a common basis whether from a theoretical or a methodological point of view.

In the (specific) field of human motor control science, this complex system approach based on the study of the links between the elements rather than the analysis of the elements in an isolated way has been of increasing interest for many years (Sleimen-Malkoun et al., 2014; Delignières & Marmelat, 2012; Diniz et al., 2011; Wijnants et al., 2009). Indeed, earlier approaches proposed in this field (isolated component analysis), can be complemented by the analysis of their relationships to have a more precise overview of the operation of the systems. In this sense, researchers have generally analysed the performance produced during a task using measures like the two first statistical moments (mean and standard deviation), thus considering that data distributions are Gaussian throughout time or repetitions. This approach does not make it possible to study the links (or dependencies) between the successive data obtained. For example, for a simple finger-tapping task, the accuracy (performance) of the participant could be investigated using the lag between the metronome (external cue) and the finger tap (motor behavior) or the drift for a synchronization-continuation task. High variability or deviation from the initial tempo is associated with a poor performance (Semjen et al., 2000; Repp, 2005).

Although these standard statistical analyzes are important, such measures are not directly related to the dynamics of the system and consider that trial-to-trial correlations are absent. In fact, previous researches have demonstrated that serial correlations observed in several human movement tasks contained a special kind of correlations known as $1/f$ noise or fractal process (Box 1; Gilden et al., 1995; Wagenmakers et al., 2004). This process implies that the time series are composed of so-called long-range correlations (LRC) between successive values. In other words, if the previous values tend to increase, there is a high probability that the current value will follow this trend (and reversely for a decrease). It has been proposed that the ubiquitous presence of these long-range correlations in time series is the signature of systems

in which the dynamics are dominated by a rich set of multi-scale interactions between their elements (Kello et al., 2007). A system as complex as the human organism will therefore produce long-range correlations in many situations. Nevertheless, although these properties reflect a complex system that is healthy, we can ask ourselves the question of what a pathology would entail in this organization, in a complementary way, if the presence of these LRCs would be directly related to this specific organization and therefore present a health marker potential.

In a relatively theoretical way, and in view of the properties of the complex systems described above, a loss of complexity can initially be expressed through a loss of elements that compose it. It seems relatively simple to imagine that, although the system is composed of a very large number of elements, a significant loss of these elements will result in limited reorganization capabilities. It is, for example, the often proposed hypothesis about the neuronal loss of elderly people, which would then lead to lower motor and/or cognitive capacities (Morisson & Hof, 1997). Nevertheless, complex systems, when only taking into account an approach based on its components, are not composed of elements of equal weight. Some of these components (as we will see for the brain especially) are defined as “hubs”, hyper-connected and essential elements, which can be considered as the minimum basis of any system. An “attack” on these hubs would be more damaging because occupying a larger space and more important functions than others.

Indeed, given the above consideration, the functional properties of the system are not limited to its components (i.e., aggregated complexity). The loss of complexity could be understood in two ways. First, a reduction in the strength of the links between the elements and, second a loss of elements resulting in a decrease in the number of links within the system (Figure 1B).

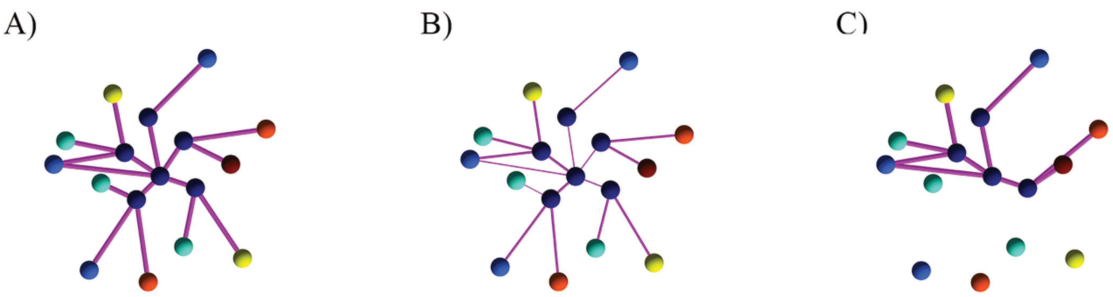

Figure 1B: Hypothesis approach of the loss of complexity. A) A complex system composed of multiple links between elements. B) A loss of complexity due to a decrease of the strength of links between elements. C) A loss of complexity due to the loss of elements, which results in a smaller number of links.

Finally, since these links can be considered as exchanges of information with dynamic properties, the loss of complexity of systems can also be due to a modification in information exchanges that becomes too continuous (rigid) or too random (chaotic). We will see especially at the level of the brain that the recent advances in neuroimaging make it possible to tackle the temporal evolution of the organization of neural networks rather than taking a single snap.

Considering humans as a complex system has led many researchers to better understand the possible loss of complexity of the system with age or diseased. This research work, often conducted in a clinical context, has focused on the distinction between groups of healthy subjects versus pathological or aging population. The approach here is to consider a healthy subject as being at an optimal level of complexity (Figure 1C). Conversely, pathology or aging should lead to a loss of system complexity towards excessive order or disorder depending on the level of impairment (Goldberger et al., 2002; Lipsitz, 2002; Vaillancourt & Newell 2002).

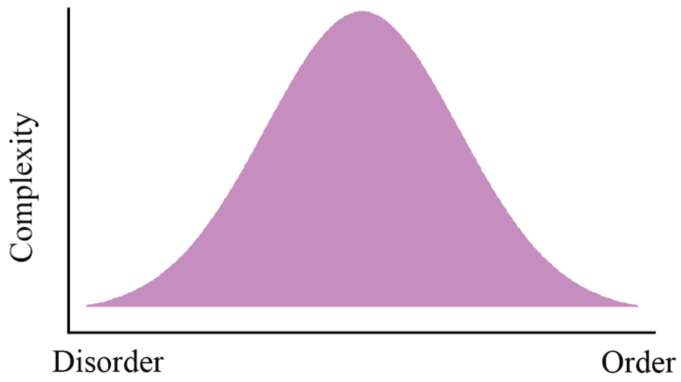

Figure 1C: The possible continuum of the complexity evolution. X-axis represents the evolution of the complexity from disorder (low predictability) to order (high predictability). Y-axis represents the level of complexity. An optimal complexity is at the top of the curve. Adapted from Stergiou & Decker (2011).

1.2 The loss of fractal properties

Due to the ubiquitous phenomenon of long-range correlations in various tasks it seems relatively understandable that teams of researchers have been interested in the possible origin of fractal processes within the central nervous system (Pritchard, 1992; Wink et al., 2008; Allegrini et al., 2009). It's not surprising then that these authors investigated the evolution of LRC in pathological populations who develop neurological impairment. For example, Parkinson's disease could be a clinical model to study the importance of the basal ganglia, which have been shown to be one of the most affected parts of the brain due to a lack of dopamine. In addition, the basal ganglia are a potential production center for the sensorimotor rhythm (Benoit et al., 2014). Others suggested that the cerebellum could be considered as the "time keeper" of the brain (Ivry et al., 1988, 1997) and *per se* a cerebellar stroke should decrease the presence of LRC in timing time series. Nevertheless, to the extent that these approaches have the advantage to wanting to localize the timing processes, some limitations could be highlighted due to the complex organization of the brain. The behavior of a system like the brain results from multiple interactions between multiple subcomponents acting at multiple time scales (Kello et al., 2007; van Orden et al., 2003). Studying an element in isolation remains reductive especially since these approaches do not generally take into account the possible temporal evolution in the series studies.

The tools and methods currently available make it possible to understand in an ever more precise way the functioning of each element of the biological systems as well as their interrelations. However, it seems necessary to try to find out simpler markers usable on a daily basis to reflect the complexity of systems at a macroscopic behavioral level. A fractal approach to complex systems has been promising for many years. This approach is based on the assumption that time series are produced by complex systems are the result of an optimal interaction between elements and sub-systems that constitute them (Kello et al., 2007).

The distinction between healthy and pathological subjects was highlighted in many contexts and helped to increase hope to discovering a health marker. For example, loss of LRC in heart rate dynamics has been shown in subjects with congestive heart failure (excessive regularity) and cardiac arrhythmia (uncorrelated randomness) compared to healthy subjects (Peng et al., 1995; Golderger et al., 2002). At the macro scale (closer to the current field of study), the study of the loss of complexity was initiated by work done on the inter stride intervals when

walking. Hausdorff et al. (1997) showed an alteration of LRC during walking in the elderly compared to young healthy subjects and in people with Huntington's disease compared with disease-free controls. Following these seminal studies, many experimental proofs followed this outcome in several diseases and many different tasks. It is the case in postural oscillations in aging (Blaszczyk & Klonowski, 2001), gait dynamics in Parkinson's disease (Hausdorff et al., 2009), serial reaction time in attention deficit disorder (Gilden & Hancock, 2007), the brain dynamics in Alzheimer's disease (Gomez et al., 2009), people suffering from depression (Pezard et al., 2001), or epileptic subjects (Babloyantz et al., 1989). All these studies taken together allowed to develop the "theory" of the loss of complexity with both age and disease and thus the hope of finding a relatively simple marker of health (i.e., LRC) and likely applicable to many pathologies.

Nevertheless, this multiple empirical evidence also points out some limitations to acknowledge. Although these authors generally consider that fractal time series are commonly produced by healthy subjects, this phenomenon does not allow a precise understanding of the origins of these properties. This approach generally considers that the loss (or decrease) of long-range correlation with pathology reflects a decrease in the adaptability potential caused by a loss of complexity of the system. Pathology leads to a decrease in the ability to perform tasks correctly or not. Can all the pathologies studied (e.g. Parkinson's, Huntington's, cardiac arrhythmia) really have common properties? The causes of these pathologies are diverse and do not affect the same functional subsystems. Let us take here two examples of pathologies that mainly affect the brain. Parkinson's disease is generally presented as a dopamine deficiency including the basal ganglia (Obeso et al., 2000). Patients with Alzheimer's disease show a decrease in glutaminergic activity in the frontal lobe compared to healthy elderly subjects (Smith et al., 1991). The modification of the temporal correlations in the time series of gait produced by these two types of pathology compared to healthy subjects therefore raises questions (e.g. Choi et al., 2011; Hausdorff et al., 2009). Although it make it possible to discriminate against pathological populations, this approach has certain limitations particularly in clinical settings. The hope of using this approach in clinical routine therefore requires comparing this empirical evidence with more fundamental approaches, which could lead to a better understanding of the underlying process of this ubiquitous character. Furthermore, the loss of complexity with age and disease was more often studied through subjects with so-called "central" suffering. Nevertheless, the studies presented previously (e.g. Blaszczyk & Klonowski, 2001, Hausdorff et al., 2009 Gilden & Hancock, 2007, Gomez

et al., 2009), have investigated either macroscopic behavioral variables or cerebral signals without making a direct link between these two different levels of observation. The question arises as whether the variables studied in motor/cognitive tasks reflect an overall suffering on the entire system or a specific subsystem potentially located in the brain.

A possible confounding factor to understand the functional meaning of the loss of complexity can be highlighted especially based on the study of Manor et al. (2010). Indeed, may consider that for an organism presenting an age-induced deficit or pathology, the realization of a task will require an increased control to compensate for this deficit. The subjects will predominantly use the modalities that the pathologie has not reached. They would also pay a careful attention to the reached modalities in order to continue the sensory information integration, which are necessary for the task realization. The authors studied the postural sway dynamics during quiet standing in four groups of elderly subjects: controls (no impairment), visual impairment only, somatosensory impairment only, and combined impairments. Their results have showed a higher complexity in the control group compared with other groups; subjects in the combined impairments group had the lowest complexity value. Manor et al. concluded that the degree of complexity is associated to the subject's adaptive capacity. Low physiological complexity may indicate a system that is less adaptive to external perturbations. This type of approach can also be understood through locomotor tasks such as walking. Many studies have investigated the effect of a dual task (usually cognitive) on walking parameters in a large number of conditions, such as Parkinson's disease (O'Shea et al., 2002), Alzheimer's disease (Muir et al., 2012), stroke (Yang et al., 2007; Plummer-d'Amato et al., 2008). This was also extensively performed in healthy elderly fallers (Toulotte et al., 2006) and with aging for example (Hollman et al., 2007; Beauchet et al., 2005). All these studies taken together showed a more pronounced decrease in performance in pathological subjects than in control suggesting a decrease in the adaptability potential for these populations. Nevertheless, although these authors consider that they analyze the adaptability of the system as a whole, we can ask ourselves a question about the possibility that these measures would rather reflect the adaptation of the subject in the realization of a given task and in a given context, rather than the system itself.

Because adaptation has a variety of meanings that are different in various fields and disciplines, we should define what we consider as adaptation in this dissertation. Our approach considers the adaptation of a system as: "Adaptation is the change by which

organisms surmount the challenges to life" (Lasker, 1969). In this sense, adaptation is a modification in either structure or function that enables an organism to survive. Adaptation could then be seen at a particular physiological location of the human (e.g. brain area plasticity) or at the whole individual. This definition brings us to draw a parallel with the notion of evolvability proposed in the literature (Whitacre, 2010), which is considered as "the capacity of the system to innovate". Going hand in hand, we define adaptability as the ability to maintain a state (in our dissertation a motor performance) by facing internal or external constraints on the system. This definition refers to the robustness property of the system. The two notions of adaptation and adaptability are closely linked and can in some sense be conceived as antithetical. On the one hand, the system should face to external constraints while continuing for example to perform the initial task. On the other hand, when the constraints are too (present) important, the system must navigate between new possible configurations to adapt and respond. A complex system is then a composition between functional properties of robustness and evolvability (Figure 1D).

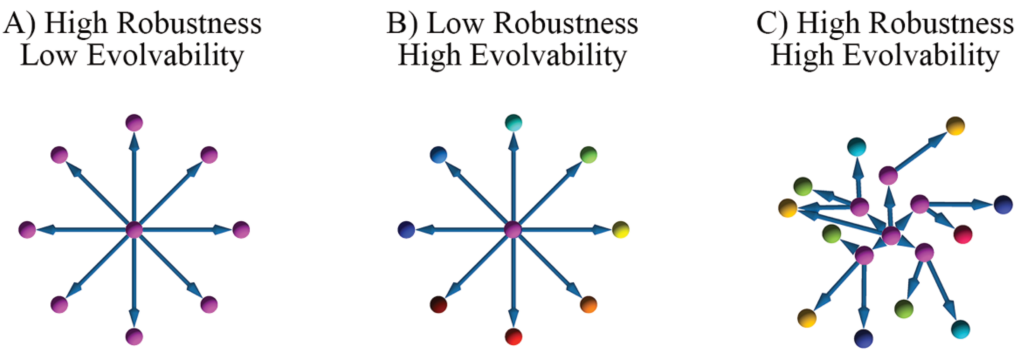

Figure 1D: Main possible configurations of a system. a) A system with high robustness but low evolvability, b) a system with low robustness and high evolvability c) a complex system composed of high robustness and high evolvability. Central node is the system. Colours represent the strategy proposed. The same colour of system implies a strategy known to perform the task. A different color implies that the system should innovate to respond to constraints.

While authors generally consider a direct link between the proposed analyzes and the complexity of the underlying system, there is still some shadow in the real meaning of the loss of complexity, particularly with regard to the current proposed experimental paradigms. The loss of complexity is generally evidenced concomitantly with a decrease in performance

measures in the proposed experimental paradigms. Nevertheless, the link between the robustness property of complex systems and/or their evolving capabilities is not directly brought to light. Experimental evidences are therefore indirect and there is possibly a confounding factor in the actual significance of the presence of long-range correlations (or their loss) in healthy or pathological subjects. In particular, we can highlight the confounding factor that we will name in our dissertation: effective adaptation. Do the variables resulting from the experimental paradigms implemented in our laboratories reflect the totality of the adaptive capacities of the underlying system or only certain states of effective adaptation to perform the task at a given moment for a single experimental condition? In this sense, our first study (Chapter 2 of this manuscript) will attempt to better understand the significance of long-range correlations, especially in terms of robustness of the system (or its adaptability), addressing healthy subjects.

Several teams from experimental psychology or human movement sciences have attempted to better understand the ubiquitous presence of LRCs and their functional meanings in a large number of experimental paradigms. The pioneering work of Gilden, Thornton and Mallon (1995), has highlighted the presence of LRC in time series coming from the reproduction of spatial and temporal intervals during a task. These authors thus showed that deviations from the mean during successive repetitions of the same task has some degree of correlation and is therefore not strictly white noise. Then, numerous experimental evidences have been reached on the presence of LRC in simple reaction time tasks (Van Horden et al., 2003; Holden, 2005), force production (Wing et al., 2004), bimanual coordination (Torre et al., 2007), synchronization with a metronome (Chen et al., 1997, Torre & Delignières, 2008), movement times in a Fitts' task (Wijnants et al., 2009, Slifkin & Eder, 2014), pointing task (Miyazaki et al., 2004), walking (Terrier et al., 2012, Dingwell and Cusumano, 2010), cycling (Warlop et al., 2013) or rowing (Den Hartigh et al. 2015).

Although these studies were conducted with young and healthy participants, the authors were able to highlight a loss of complexity (decrease in the presence of long-range correlations) during their experiments through the time series analyzes they carried out. The modification of the instructions or the experimental conditions for the realization of the task came to modify the presentation of LRC. Redundantly, the increase in experimental constraints imposed has resulted in long-range correlation changes in the time series produced. Indeed, the completion of a task with a metronome (e.g. Torre & Delignières, 2008), an imposed step

rate or the addition of a visual feedback to control the performance (e.g Warlop et al., 2013) led to worse correlated time series (occurrence of white noise). These surprising results allowed the authors to formulate the idea that the addition of non-essential feedback to achieve the task would force the system. In this sense, the optimal complexity (as reflected by LRC) could therefore be considered as the natural signature of the system, whose intrinsic fluctuations are freely expressed without major control (Kello et al., 2010).

The previous sections of this manuscript highlight some fundamental questions on the functional significance of fractal properties. On the first hand, fractal properties used to analyze the loss of complexity of any system revealed that the long-range correlations could be distorted in elderly and diseased subjects compared to healthy subjects, but also in subjects using increased feedback to perform the experimental task facing to external constraints. As a consequence, it might be difficult to distinguish whether time series complexity reflects the underlying system and its adaptability capacity or effective adaptations of the system to perform a task according to the imposed external constraints. This issue will be investigated in this dissertation.

Nevertheless, one question now results from the possible origins of the effective adaptation and the functional significance of fractal properties at the global (macroscopic) scale of observation (in our case the motor behavior). Two theoretical ways were developed in the previous literature that was named the “nomothetic perspective” and the “mechanistic perspective”. The first perspective generally considers that fractal processes are not specific of one part of the complex system (or one scale of observation) but are rather a general outcome from all components and all links between components (Van Orden et al., 2005). This approach is based on the self-organizing principle of the system and the emergence concept (Kello et al., 2010). Authors proposed that the self-organization of the system composed of multiple degrees of freedom evolves to a minimally stable state and that the multiplicative effect of the multiple scales leads to a power law (or 1/f noise, fractal process) (Bak et al., 1987). For authors, factal time series is a ubiquitous phenomenon (Gilden, 2001; Kello et al., 2008). On the other hand, the mechanistic approach driven by simulation studies (see for example the discussion of the study of Delignières & Marmelat, 2012) revealed that fractal processes could be generated by a relatively low number of components and parameters. The second mechanistic perspective follows the idea that different mechanisms can generate fractal time series, which depends on the behavior under study (i.e., the task or

the scale of observation). Globally, for the first nomothetic approach, as the fractal time series is ubiquitous, there is no reason to trying to investigate the possible functional origins of the phenomenon and any potential links between components of the system. The second mechanistic approach, opens a way to multiple and multimodal analyzis to highlight the potential link between multiple scales of observation. Although these approaches were initially proposed from a fundamental point of view and studied, thanks to computer simulations, the development of neuroimaging tools makes it possible to investigate a new track, in particular the link between the brain dynamics and the dynamics evaluated at the behavioral level (See next Section 1.3).

1.3 Linking brain and behavior in neuroscience

For nearly a century, neuroscience research works have been trying to better understand the site of the complex motor behavior generation in the brain. This fascination can be understood from a fundamental point of view but also in the possible clinical applications for a better understanding of multiple pathologies. The increasing development of neuroimaging methods has shed light on the brain-behavior links in a large number of experimental paradigms. One of the most used approaches is based on the adaptation paradigms. The concept of adaptation is the keystone to understand the organization of the human in everyday life (and the loss of adaptation in a pathological case). Much of the literature has used a simple sensorimotor task combined with neuroimaging methods to better understand the performance production of a one- or two-handed task as well as the complexity of the tasks. The initial focus of analytic strategies in human neuroimaging was on identifying reliable task-dependent signal changes. Such studies have used healthy volunteers to fundamentally understand the human organization or compared healthy versus pathological participants to explain the causal link between the changes in brain activation and the loss (or alteration) of adaptation in these motor tasks. The brain activation profile during sensorimotor task was shown in electroencephalography (EEG; Shibasaki et al., 1980; Sur & Sinha, 2009), positron emission tomography (PET; Grafton et al., 1992), functional magnetic resonance imaging (fMRI; Kim et al., 1993) and near-infrared spectroscopy (fNIRS; Holper et al., 2009; Leff et al., 2011) studies. Performing a motor task modulates/influences activation profile in specific brain areas such as the primary motor cortex (M1), supplementary motor area (SMA) and premotor area (PMA) in healthy subjects. The difficulty of the task or the force production capability was shown to lower the inter-hemispheric balance (Rao et al., 1993; Derosière et al., 2014).

Such findings were then considered as common sensorimotor markers in healthy subjects and then compared to multiple pathologies or aging. This ushered in a new prolific era named "brain mapping" and leads to the well-known statistical parametric map (SPM; Friston et al., 1995) in fMRI and fNIRS studies and topographical map in MEG and EEG studies. Nevertheless, this kind of study generally considers *a priori* that the variability corresponds to white noise both at the levels of the behavior and the brain. This kind of noise being considered as a participant error or induced by the equipment used, some filters and averaged measurements for mass univariate analyzis of brain data are commonly employed. Nevertheless, as previously indicated, this first basic approach leads to a loss of essential information for a better understanding of complex adaptive systems. Similar to the behavioral time series, brain signals extracted from EEG, fMRI and fNIRS measures were investigated using more fine-grained methods than mean or standard deviation. Mono- and multi-fractal analyzes were used to extract the complex time course of multi-frequency bands of EEG data or hemodynamic responses contained in fMRI and fNIRS signals (e.g., Eke et al., 2002, 2012; Figliola et al., 2007). In spite of efforts to link the brain and behavioral functions, approaches used in the aforementioned studies still represent an oversimplification of the real adaptations of the human brain and generally these empirical investigations did not attempt to make a direct link between observations and the underlying model making it possible to generate this kind of complex time series.

Some authors have proposed fundamental models to the functional organization of complex systems producing fractal properties at the macroscopic scale. A first approach called "self-organized criticality" was initially proposed by Van Orden and colleagues (Van Orden, Holden & Turvey, 2003; Kello et al., 2007). These authors propose that the complex system balances between numerous solutions, what they called the concept of criticality. The system is considered metastable (Kelso et al., 1995; Kelso, 2012) which means that a small perturbation at a given point in the system can lead to a global change in the system (Figure 1E). This property allows the system to explore new functions (or states), which will allow it to be flexible and therefore adaptable. This "self-organized criticality" is only possible when the system has multiple connections between its elements and between levels and therefore assumes that the importance of connections is greater than elements constituting it.

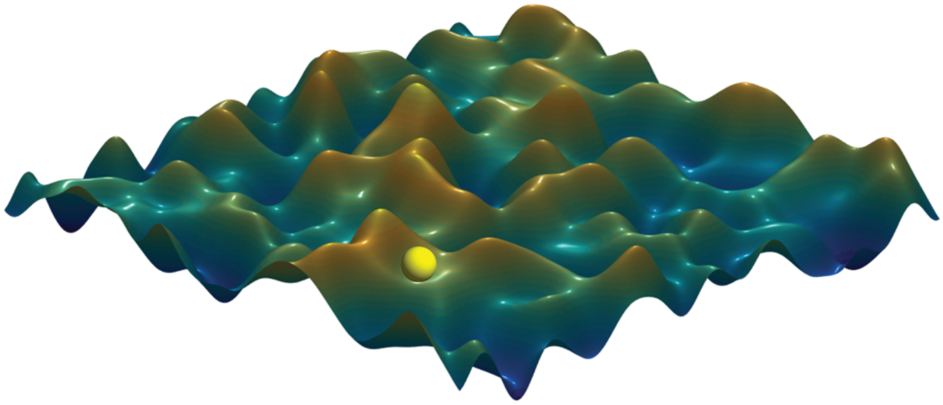

Figure 1E: 3D Modelling of the Metastability of a system. The yellow sphere represents the current state in which the system is located. A slight perturbation may allow the system to switch from one basin to another basin that modifies the state of the system. Adapted in 3D from Kelso, 2012.

An alternative approach, close to the one developed previously, is the "cascade dynamics" model (Ihlen & Vereijken, 2010). The key element proposed is that connections between scales are dependent and thus reflect some dependencies. These dependences are reflected in the exchange of information (or energy transfer) between scales. A perturbation at a small scale will influence the state of the higher scale with a multiplicative coefficient. This specific statistical dependence makes it possible to produce more complex time series (multifractals) than the series produced by the model of self-organized criticality.

Although these models are interesting, a possible third candidate would explain the presence of long-range correlations produced by complex systems. This approach was suggested by G. Tononi, O. Sporns and G. Edelman in 1999 (Tononi et al, 1999) and was called "Degeneracy". The concept of degeneracy was firstly applied to the "structure" of a system (whatever the level of observation is). Therefore, it does not refer to external events that may occur on the system. Nevertheless, degeneracy is shown as a biological property and is defined as follows: *"A many to one relationship. Distinct elements could perform the same function"*. The above property is found at the biological level in the genetic code (DNA), genes, synaptic connections, the connectivity of the cortical areas and the human movements (Edelman & Gally, 2001). In order to better understand the concept of degeneracy, which is

partially independent of that of degeneration, we can tackle it with the concept of redundancy. The redundancy of a system is often considered as a sign of robustness (Whitacre, 2012; Whitacre & Bender, 2010). From an engineering point of view, multiplying the communication channels in parallel allows, in case of failure of one element, a propagation of the signal through the redundant channels. For example, the computer on board of Curiosity to explore Mars (boarding of two computers with the RAD750 PowerPC microprocessor but only one being active at a time) allows, if a processor or a computer fails, to level the problem; the second computer will take over. It is from these properties that degeneracy is also commonly called partial redundancy. The fact of commonly pointing to degeneracy as partial redundancy is due to these properties. Furthermore, degeneracy of systems is considered as a prerequisite to allow for robustness and evolvability that are two essential properties of complex adaptive systems (see Section 1.2). Taking into account the degeneracy of the biological system, we argue that the system could use multiple functional configurations during a task to perform the same function (functional intermittence) which is one of the essential properties implemented both at the level of the brain but also of the behavior (Kelso & DeGusman, 1991; Oullier & Kelso, 2006; Tognoli & Kelso, 2014). Therefore, the long-range correlation properties of the biological series studied could be a reflection of the degeneracy capabilities involved in the performance of a task. A decrease or loss of complexity could be linked (at least in part) to a decrease in the degeneracy of the system. Thus, we can hypothesize that fewer alternative functional configurations would be available implying less adaptability to internal or external constraints.

Since the pioneer works of Santiago R.Y Cajal in the early 1900's, the brain is generally considered as the complex system *par excellence* for neuroscientists. However, a purely regional and univariate approach does not explicitly address the possibility that communication between distributed populations of cortical neurons contributes to cognition and behavior. Such contributions may occur even in the absence of obvious changes in regional brain activation profile (Misic & Sporns, 2016). Nevertheless, since two decades, connections and interactions among brain areas (at the macroscale) are increasingly recognized as the basis for complex cognitive and behavioral functions (Achard & Bullmore, 2007). From a theoretical point of view, the brain reflects both segregation (some parts are dedicated for a specialized function) and integration (exchange of information between multiple areas) (Friston, 1994; Park & Friston, 2013). Recently there has been an exponential

development of neuroimaging tools aiming to monitor multiple brain areas with greater precision: including the increased in the temporal and spatial resolution of fMRI and the ability to cover the entire scalp of the brain with multiple EEG electrodes. Combined with the development of computer sciences, researchers can study the brain as a (complex) network. Within this context, we have to emphasize here two different approaches in brain network studies (both are in any case highly linked and complementary).

First, the so-called "structural" connectivity tries to map the complete structure of the brain (named the Connectome; Sporns, 2005) using for example Diffusion-weighted magnetic resonance imaging or simulations. It is clear that the total description of the brain is not yet possible with an organ composed of 10^{11} neurons and an estimation of 10^{5} kilometres of axonal projections forming a matrix of 10^{100} bins (Papo et al., 2014). A widely used model to answer fundamental questions concerning the structural organization of the brain is the nematode *Caernorhabditis Elegans* composed of "only" 302 neuronal cells (Koch & Laurent, 1999).

Second, some neuroimaging methods like EEG and MEG (in the electric and magnetic domains, respectively) as well as fMRI and fNIRS (methods based on the cerebral blood flow changes) allow researchers to non-invasively examine the "functional connectivity". The functional connectivity is defined as the statistical dependency between two (bivariate) or more (multivariate) time series extracted from these methods like frequency bands (alpha, beta, etc. in EEG/MEG) or blood oxygen level dependent signal (BOLD in fMRI) following the neurovascular coupling during brain activation. The statistical dependence between time series linking cortical areas was initially achieved with what we now call a "seed based" approach. This method requires the researcher to select an *a priori* region of interest (ROI) and then quantify the similarity (e.g. correlation, coherence) between this ROI and all other regions investigated. Nevertheless, this *a priori* can sometimes lead to certain limits when the literature does not allow making strong assumptions and restricts the network topology to an oversimplification. Today, realizing a whole brain functional connectivity analyzis is commonly performed thanks in particular to the development of computing power and methodological tools. These whole brain approaches allow to realize all the possible combinations of connections (resulting in a noticeable increase of the data to be treated statistically) and thus to extract a more realistic map of the brain networks (Figure 1F). Although the first studies using functional connectivity tried to analyze the brain network organization at rest and during the execution of a motor or cognitive task (e.g. Biswal et al.,

1995), the major craze was developed for these studies during the so-called resting state conditions.

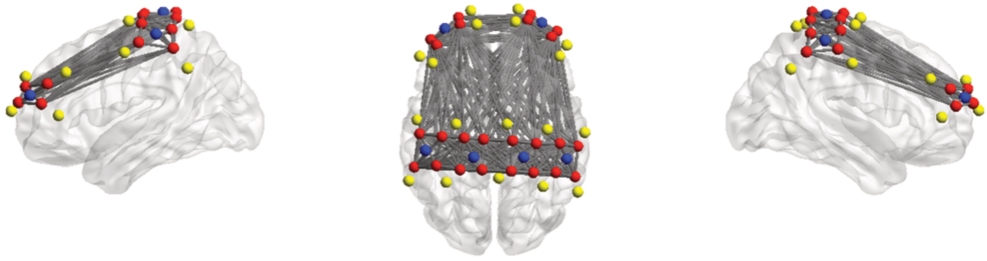

Figure 1F: Example of the increasing level of computational complication using functional connectivity analyzis. The number of links (grey lines) increases exponentially with the number of areas that the researchers include. Personal data extracted from Studies 2 and 3 of this dissertation. Spheres represent both optodes (yellow and blue) and channels (red) location from fNIRS devices used.

Although many studies have been interested in the functional connections between different regions of the brain and have shed new light on cerebral functioning at rest or during cognitive/motor tasks, it is recently that first empirical evidences of the dynamics of connections were highlighted (Chang & Glover, 2010; Hutchinson et al., 2013). As we have seen previously, complex systems have both many connections between elements and dynamic properties (including temporal evolution) that allow them to modify their functional organization to meet internal and/or external constraints. It therefore seems essential, in view of the models proposed and in particular the concept of degeneracy, to try to experimentally understand the link between adaptations from a motor control point of view and the dynamical organization at the level of the brain in a joint way.

1.4 Objectives of this dissertation

The literature presented in this introductory chapter highlights that two different explanations are put forward for the loss of complexity of the systems expressed through the correlations decrease in long-range correlations. While the loss of complexity was demonstrated in pathological subjects compared to healthy subjects, other studies have shown changes in LRC's depending on the constraints imposed on participants. Although these studies are generally dissociated in the literature, we can hypothesize a possible confounding factor linking these two approaches. Indeed, we can think that aging participants or subjects with

pathologies may set up an increased involvement of feedback to best accomplish the task, potentially with an equivalent level of performance of healthy subjects. Therefore, the overall objective of this dissertation is to highlight the functional significance of fractal analyzes regarding the actual adaptation (effective adaptation) implemented to perform a sensorimotor task under various external constraints.

This work is divided in three parts, which all describe components of the primary aim. The first part of the dissertation investigates the functional significance of mono- and multi-fractal analyzis during a finger-tapping task under various conditions (Chapter 2). In chapter 3, concurrent changes of brain functional connectivity and motor variability are being compared when adapting to task constraints. Chapter 4 explores the dynamics of the human brain network revealed by time-frequency effective connectivity in fNIRS. Figure 1G represents the links between all key words investigated or discussed throughout this dissertation.

This work addressed two main questions. These were:

- Are the long-range correlations present in a sensorimotor task reflect effective adaptations or the adaptability of the subject?

- Is the capacity of effective adaptation of the subjects investigated at the level of behavior related to the cerebral dynamics during the realization of the task?

It was hypothesised that:

- Mono- and multi-fractal analyzes reflect two distinct properties of the system under study. Mono-fractal analyzes reflect the adaptability of the system while the multi- fractal properties reflect the effective adaptation of the subject to achieve the task despite the imposed constraints.

- Multi-fractal analyzes would reflect the dynamics of the degeneracy of brain networks implemented as a function of the imposed constraints.

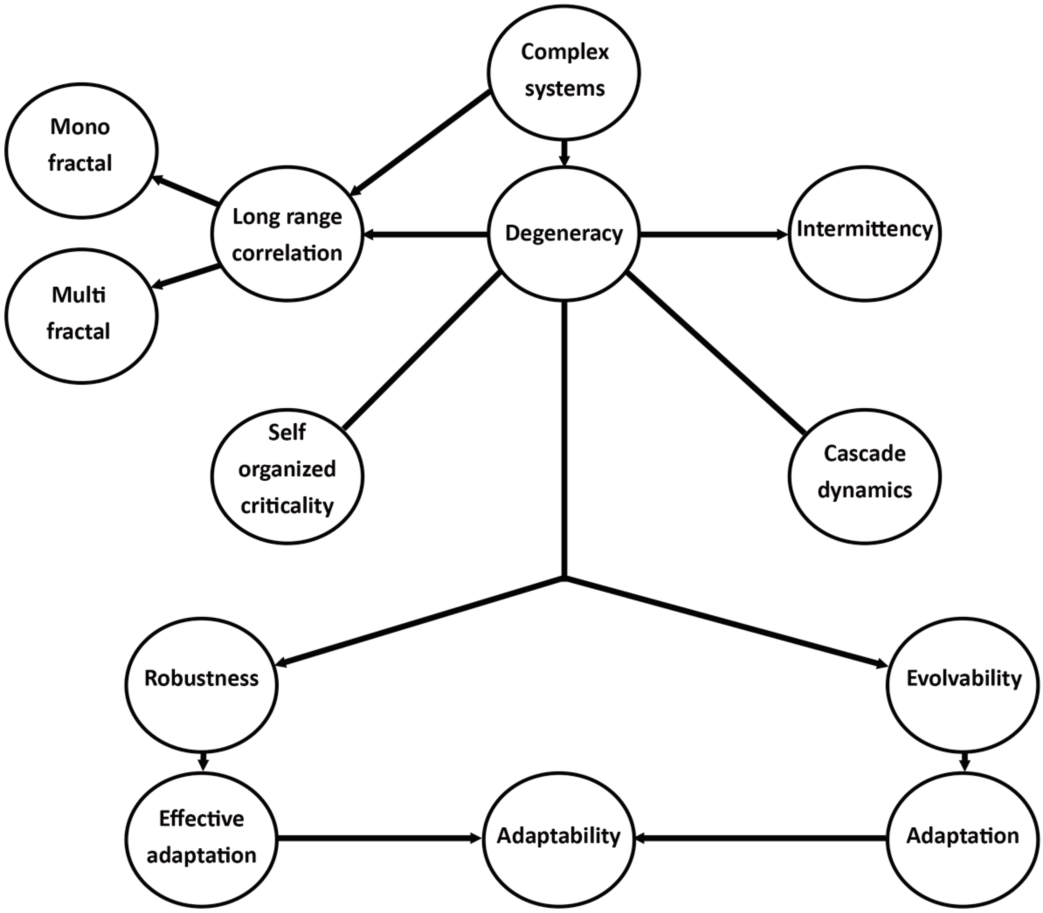

Figure 1G: Diagram showing the links between the different keywords constituting the theoretical framework of this dissertation. This diagram will be the guideline between the studies presented as well as all through the discussion.

Box 1

Fractals

"Fractals are everywhere"

https://www.youtube.com/watch?v=Tpsu2uz9rCE

Although this statement is a bit exaggerated, it appears that fractal properties are ubiquitous phenomena in multiple natural and biological elements. Mandelbrot in the 70's realized that very often, Euclidean geometry does not allow accounting for the complexity of the observed forms. This approach was first developed in the field of mathematical geometry and implies an essential property that is the self-similarity. Whatever the observation scale of the object in question, it retains the same characteristics as if we observe it at a higher or lower level. A relatively explicit example of this phenomenon is expressed through the Von Koch curve (or Koch snowflake, Figure 1H) (Mandelbrot, 1983).

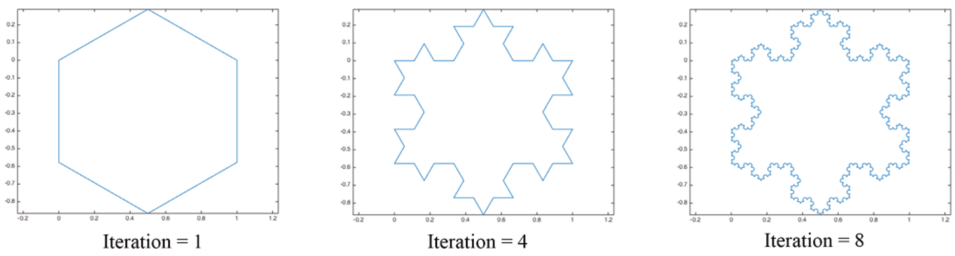

Figure 1H: Representation of Koch snowflake for iteration 1, 4 and 8.

Nevertheless this phenomenon is not limited to a specific case of iterative mathematic but is also found for example in mountain peaks, torrents or from a biological point of view in vascular branching or DNA. More surprisingly, these fractal analyzes have also been studied in the properties of chocolate surface (Pedreschi, Aguilera & Brown, 2002), the United States Coastlines (Jiang & Plotnick, 1998) and Hard Disk surface (Kennedy et al., 1999). Surprisingly, this (statistical) self-similarity property is also commonly found in biological time series. In other words, the fluctuations seem statisticaly the same, whether viewed at the scale of the year, the week, the hour or the minute. This is different from a simulated sinusoidal time series that will be identical to a single single frequency. A second property of time series highlighted in the literature is the presence of long-range correlations. The successive data constituting the series are more or less correlated with each other. Their autocorrelation decreases slowly over time. On the contrary, a series of white noise (totally random series) will present an autocorrelation that will decrease very quickly (close to zero). Successive data will not be related to each other over time. More simply, in time series with long-range correlations (called fractals, 1/f noise or pink noise), if the previous values have a tendency to increase, the current value will be more likely to continue to increase as well (see Figure 1I). This property, which links the data between them, will therefore limit the aberrated values (which will be very rare). As a result, the fractal series will be composed of values according to a power law. Small events (small disturbances) will be more numerous than major events. In other words, the amplitude is inversely proportional to the frequency.

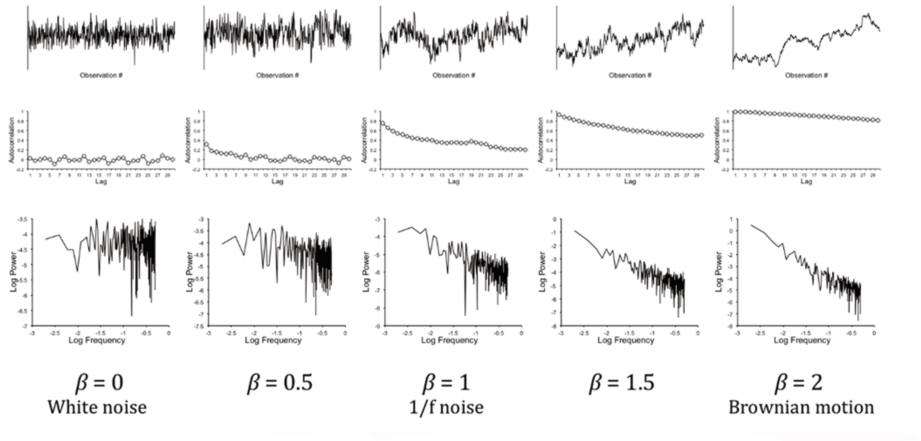

Figure 1I: Distinction between White noise, 1/f noise and Brownian motion. From the White noise (left) to the Brownian motion (right), correlations in time series increased as reflect by the auto-correlation plots (middle) and the Log Power spectrum density (below). 1/f noise (pink noise, fractal time series) is represented in the middle column. This figure is extracted from Delignières & Marmelat (2012).

Many methods have therefore been developed to account for the presence of these long-range correlations in the time series. One of the most common and relatively robust was proposed at first by Peng (1995) and applied to heartbeat time series. Nevertheless, this method considers that long-range correlations are homogeneous over time in the time series. The dynamic properties of biological systems allow them to make the assumption that these correlations will fluctuate between moments when the correlations between successive data are relatively limited and others relatively long. For this purpose, multi-fractal analyzes were developed to account for these fluctuations, notably by Kantehlard's work in 2002 (see also Ihlen, 2012 for a comprehensive matlab tutorial). Multi-fractal detrended fluctuation analyzis (see Chapters 2 and 3) will therefore analyze the dependence between successive data at different time scales and will result in output by a multitude of exhibitors. The difference between the weakest exponents and the highest exponents will reflect the multi-fractality level of the time series. These two analyzes (mono- and multi-fractals) will be at the heart of the first two articles proposed in this work and in particular their meanings when representing the underlying system.

Chapter 2

Adaptability or adaptation: functional meaning of fractal properties

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Manuscript in preparation

Results presented in this study are preliminary.

Abstract:

The loss of complexity in bio-behavioral variables sees two discordant approaches which coexist: the loss of complexity with age and disease, and the loss of complexity due to increased sensorimotor control. Thus, the loss of complexity appears as an ambivalent phenomenon. The purpose of this study is to specify these functional meaning. Eight groups of subjects performed a self-paced finger-tapping task under incremental feedback deprivation (auditory and/or visual and or proprioceptive). A deafferented subject (IW) was also included. The literature indicates that unlike visual and auditory feedback, only deprivation of proprioception may possibly be a constraint for tapping performance. We analyzed the joint evolution of the performance as well as the mono-fractal and multi-fractal properties of the series of inter-tap intervals produced. Preliminary results show an identical pattern of results for performance and the mono-fractal exponent, both being degraded for IW only. On the other hand, the level of multi-fractality increases progressively with the number of feedbacks deleted. Given the independent evolution of mono- and multi-fractal properties, we discuss their respective meanings in terms of effective adaptation and adaptability of the system.

Keywords: adaptation, fractals, DFA, MFDFA, tapping, feedback

1. Introduction

Since the advent of neuroscience, the heart of much research has been to find health markers in order to discriminate pathological from healthy populations. In this sense, a relatively recent discipline is interested in the analysis of time series produced at a macroscale level (e.g. motor control output). While the first studies multiplied the repetitions of the same experimental condition and then extracted the average value or variability, this approach has some shortcomings considering that repetitions between successive values or events are independent in time. However, this assumption is more the exception rather than the rule (Slifkin & Newell, 1998) and a temporal dependence between successive events were shown as a valid approach to discriminate much pathology through a wide range of time series analyzed. One of the first and most understandable examples is from works of heartbeat time series (Peng et al., 1995). At first, these studies show that beat-to-beat fluctuations in heart rate intervals follow a power law and display long-range correlation in time (or 1/f noise, pink noise, fractal process). This was followed by the investigation of these statistical properties into time series of pathological subjects such as those with an arrhythmia or congestive heart failure (Goldberger et al., 2002). Time series from pathological populations revealed a decrease in these long-range correlations, the temporal dependence on events was less dependent on each other, close to white noise. This has led to the search of many clinical teams for and identification of long-range correlations (and its decrease) in much pathology and experimental paradigms. These researches have highlighted the possibility to discriminate healthy subject to pathological or aging population in gait (Huntington and Parkinson disease; Hausdorff et al., 1997), postural sway (aging; Blaszczyk & Klonowski, 2001), reaction time (ADHD; Gilden & Hancock, 2007) and brain activity (Alzheimer; Gomez et al., 2009) for example.

Nevertheless, these studies do not reveal the possible origin of the presence of these long-range correlations in the healthy subjects and the mechanism explaining the tendency to produce white noise in the pathological populations. This notion being easily grasped at a macroscopic level of observation, the study of the human in the achievement of motor tasks would therefore make it possible to apprehend the complexity of the system by observing the time series produced. On the basis of this postulate, a deficient / pathological system, conceived as suffering a loss of complexity

due to the loss of elements or links between these elements, should be reflected in the fractal properties in the tasks produced. Nevertheless, the loss of long-range correlations was also highlighted in studies apart of any pathological context. These studies highlight a loss of long-range correlation when changing constraints on subjects in many tasks. Such evidence was thus investigated in Fitt's task (Slifkin & Eder, 2014), gait on treadmill with auditory metronome (Terrier et al., 2012; Dingwell & Cusumano, 2010) and cycling pattern with visual control (Warlop et al., 2013). As subjects included in these studies are young healthy volunteers, long-range correlations could then reflect the natural signature of the healthy system performing a task without undue constraints (Kello et al., 2007; 2010). A tendency to produce white noise time series would reflect increased biomechanical or cognitive control of the subjects, thus preventing them from performing additional tasks (for example in very strong double task paradigms). This proposal is not contradictory with the theory of the loss of complexity with aging or pathology. Indeed, much pathology and aging are generally related to a loss of sensory feedback directly due to the pathology or with cortical reorganization in visual and/or auditory and/or proprioception (Li & Lindenberger, 2002).

One interesting study proposed by Manor et al., 2010, crossed both kind of approach proposed above that are generally segregate in a postural control task. Aging participants were classified in groups of sensory impairment as control (aging participants without impairment) and with visual and/or somatosensory impairment and performed a postural task with a dual task. Authors highlight that group with a loss of sensorial feedback product less long-range correlation in postural control time series and therefore postulated that complexity analysis could reflect the capacity to the system to adapt in tasks.

Nevertheless, there is no clear distinction in this study as to the possible confounding factor between the adaptive capacities of a system that can be divided into two subparts. On the one hand, the adaptability of a system can be seen as being very strongly related to robustness properties. Depending on the internal or external constraints imposed on the system, the system will be reorganized from a functional point of view to continue to maintain the level of performance required in the performance of the task. However, in this study the authors do not directly

manipulate feedback such as vision or having deficiencies of these systems following pathologies, the study does not therefore make it possible to discriminate if the loss of complexity expressed through the fractal analyzes would reflect a deficient system or the implication of different feedbacks in the accomplishment of the task.

Given the above considerations, the purpose of the study is to directly manipulate the feedbacks in the realization of a motor task in healthy subjects to allow to clearly identifying if the implication of these feedbacks (and their decrease) will influence the fractal properties, which result from it. In this sense, we will use mono- and multi-fractal analysis as the two approaches could highlight different properties of the system (Ihlen & Vereijken, 2013). One the first hand, mono-fractal properties (e.g. Detrended fluctuation analysis) reflect a global and unique exponent considering that long-range correlations are homogeneous in time and reflect a general property of complex systems. On the other hand multi-proprioception. The subjects fractal analysis (e.g. Multi-fractal detrended fluctuation analysis) could reflect the effective adaptation of the system under constraints reflecting changes in correlation at short or long time scales.

Following from the above, we hypothesized that healthy subjects performing a simple finger-tapping task will therefore reflected a same mono-fractal exponent independent of the external constraints imposed to performed the task. On the other hand, multi-fractality should evolve with the external constraints (the number of feedback deprived, namely auditory and/or visual feedback) imposed to perform the task. Additionally, the suppression of the proprioception (assessed with the help of an anesthetic block and a deafferrented subject) should reflect a decrease in all variables (performance, mono-fractal and multi-fractal) compared to other groups, as the deprivation of proprioception was highlight as a putative constraint in a finger-tapping task (Aschersleben et al., 2002).

2. Materials and methods

2.1 Participants

2.1.1 Healthy participants

Ninety-four healthy young volunteers took part in the study (fifty-three men, fourty one women, 24.5 ± 5.2 year of age). All participants signed a written informed consent before participating in the study. All participants performed the study with their self-reported dominant hand (heighty nine right handed and five left handed) and reported normal hearing, normal or corrected vision and normal proprioception. None showed any sign of neurological disease, nor reported extensive practice in music. All procedures complied with the Declaration of Helsinki for human experimentation.

2.1.2 Deafferented participant

One deafferented participant (IW) was include in the study. IW is subject of complete loss of cutaneous touch, kinematics and movement/position sense. Pain and temperature sensations are clinically spared, and there was no motor nerve impairment due to a large sensory-fiber peripheral neuronopathy below C3 occurred at age 19. Nevertheless, after a clinical rehabilitation IW was able to move by visually monitoring his movements.

2.2 Experimental design and procedure

The experimental design was an independent-group design with the experimental factor being the numbers of sensorial feedbacks the participants were deprived from and at a second level the sensorial modality. Participants were randomized to one of the height following conditions: (i) no feedback deprivation (Control), (ii) deprivation of one feedback, visual, or auditory, or proprioceptive (-1 FBa, -1 FBv, -1FBp); (iii) simultaneous deprivation of two feedbacks, visual and auditory, or visual and proprioceptive, or auditory and proprioceptive (-2 FBva, -2 FBvp, -2 FBap); (iv) simultaneous deprivation of three feedbacks, visual, auditory and proprioceptive (-3 FB). IW was deprived of the visual and auditory feedback in addition to cutaneous touch and kinematics loss due to the pathology. Participants were deprived of visual and auditory feedbacks using a sleeping mask and ear defenders, respectively. The proprioceptive feedback was prevented by anesthetic sensory block (injection of ropivacaïne, ≈ 7.5 mg/ml) at the three nerves of the wrist (ulnar, medial, radial) with a volume of 2 ml per nerve. Each participant performed three tapping trials in the assigned conditions. As mentioned above, none of the visual or auditory deprivations should alter tapping

performance (Repp & Su, 2013; Aschersleben & Prinz, 1997, 1995) however the loss of proprioception (with anesthetic bloc or for IW) should alter the performance (Aschersleben et al., 2002, 2006).

2.3 The tapping task

The experiment was conducted in a quiet room. Participants were sitting comfortably on an adjustable chair, with their dominant side forearm and palm of the hand resting on a customized plinth (570 × 160 × 50 mm) on a table in front of them. Subjects realized a tapping task according to a conventional synchronization-continuation paradigm (Wing and Kristofferson, 1973; Vergotte et al., 2017): during the initial synchronization phase, the tempo was prescribed by a PC-driven auditory metronome delivering 20 signals at a frequency of 1.5 Hz (0.666 s inter-tap intervals), known as a comfortable tapping frequency (Fraisse, 1966; Torre & Delignières, 2008). Once the metronome stopped, participants had to continue tapping by maintaining the prescribed tempo as accurately and regularly as possible for the whole trial duration. The duration of each trial was set to 6 minutes 40 seconds so as to ensure a sufficient number of inter-tap intervals to be submitted to subsequent fractal analysis (Eke et al., 2012; Delignières et al., 2006). Between each of the three trials, participants had a 2-min rest.

2.4 Data collection

Movements of the index finger were captured using a single-axis accelerometer (15 × 15 mm) fixed on the nail so as to minimize possible device-induced sensorial feedbacks. Acceleration data were collected using a Labjack U12 device and stored via its software (LJStream v1.07). The sampling rate was 300 Hz.

2.5 Data analysis

2.5.1 Tapping performance

Raw acceleration data were first low-pass filtered using a Butterworth zero-phase digital filter (Frequency = 15 Hz). Then, a MATLAB in-house script (MATLAB 2014b, The MathWorks) for peak detection was used to extract the onsets of the subsequent finger taps. Series of inter-tap intervals (ITI) were then computed as the differences between subsequent tap times. For each trial, the first twenty ITI (corresponding to the

synchronization phase) were discarded, and series of 512 ITI in the continuation phase were retained for further analyses. For each ITI series, we computed the typical performance variables used in tapping studies (Billon et al., 1996; Repp & Su, 2013), namely the mean, the coefficient of variation (CV) and the linear drift over the trial duration.

2.5.2 Fractal analysis

Fractal time series are basically characterized by fluctuations with scale invariant structure (*i.e.,* obeying a power law distribution $X(ct) = c^{H}X(t)$, where X is the signal, c is a constant, H is the fractal exponent) and temporal long-range correlations (meaning the autocorrelation function of the time series decays as a power-law without falling to zero). To analyze the fractal properties of ITI series, we used the mono-fractal Detrended fluctuation analysis (DFA, Peng et al, 1995) and the Multifractal Detrended Fluctuation Analysis (MFDFA, Ihlen, 2012; Kantelhardt et al., 2002). In short, DFA exploits the diffusion properties of the time series, analyzing the relationship between the average amplitude of fluctuations and the size of the observation window within which these fluctuations are measured. For fractal series, a power-relationship characterized by the mono-fractal exponent $\alpha \in [0, 2]$ is expected: in particular, for $\alpha = 0.5$ the series is white noise, for $\alpha = 1$, the series is so-called *1/f noise*, and for $0.5 < \alpha < 1$ the series is considered stationary and containing persistent long-range correlations. By yielding a single fractal exponent (α) characterizing the average fractal properties of a time series, the DFA assumes that the fractal properties are homogeneous over all scales of the entire time series.

However, instead of being characterized by a single homogeneous fractal exponent, time series of bio-behavioral variables are often characterized by an inhomogeneous distribution of variability (intermittent fluctuations). The fractal exponent may vary over time scales: the series is actually characterized by multiple fractal exponents (Ihlen & Vereijken, 2010) and with this viewpoint the MFDFA was developed (Ihlen, 2012; Kantelhardt et al., 2002). MFDFA basically uses the same steps as DFA, but the average amplitude of the fluctuations is calculated using q^{th} order fluctuation function, with q varying from -10 to +10 in steps of 0.5, whereas DFA computes the amplitude of fluctuations only for $q = 2$. In brief, the time series $x(i)$ is first integrated into $X(k)$ following Eq.1:

$$X(k) = \sum_{i=1}^{k}[x(i) - \bar{x}]$$

(Eq.1)

The series is then divided into N_n adjacent segments of length n. Within each segment (s = 1, ..., N_n) the local trend is then subtracted from $X(k)$. So, the amplitude of fluctuations is computed for each detrended segment according to:

$$F^2(n,s) = \frac{1}{n}\sum_{k=(s-1)n+1}^{sn}\left[X(k) - X_{n,s}(k)\right]^2$$

(Eq.2)

The variance is then averaged over all segments to obtain the q^{th} order fluctuation function:

$$F_q(n) = \left\{\frac{1}{N_n}\sum_{s=1}^{N_n}\left[F^2(n,s)\right]^{q/2}\right\}^{1/q} \quad \text{(Eq.3)}$$

If the series $x(i)$ presents fractal properties, the generalized Hurst exponent $h(q)$ is given by:

$$F_q(n) \propto n^{h(q)} \quad \text{(Eq.4)}$$

According to Kantelhardt et al. (2002), the result of MFDFA can then be converted into the classical multi-fractal formulation using simple transformations, to be finally summarized by the multi-fractal spectrum representing $F(\alpha)$ as a function of $\alpha(q)$, where $F(\alpha)$ is the fractal dimension (or dimension of the subset of the series that is characterized by α), and α is the Hölder (or singularity) exponent. Our variable of interest is the width of the multi-fractal spectrum (MF-Width), meaning the range between the minimum and maximum exponents $\alpha(q)$ characterizing the time series, which represents the degree of multi-fractality.

2.5.3 Statistical analysis

After normality testing (Lilliefors test), between-group differences were tested using ANOVA on the three tapping performance variables (mean, CV and drift of ITI series), and on mono-fractal exponent DFA (α) and multi-fractal width (MF-Width) with Bonferroni post-hoc correction. The comparison between -2FBav and IW was done by a one-sample t-test.

3. Preliminary Results

3.1 Tapping performance

3.1.1 Mean ITI

All reported results relate to control conditions, -1FBa, -1FBv and -2FBav conditions. Mean tapping performance was normally distributed for 7 of our 8 mean variables (4 conditions, 2 repetitions; $p > 0.1$). The ANOVA applied to the mean didn't showed any statistical significant difference between the frour groups ($F(3, 29) = 2.38$, $p > 0.05$) (Figure 2A left).

3.1.2 Coefficient of variation of ITI

Coefficient of variation was normally distributed for the 8 variables ($p > 0.10$). Our experimental design was thought to impose different levels of constraints to the subjects without inducing differences in tapping performance. The ANOVA didn't show any statistical difference between the four conditions ($F(3,60) = 0.704$, $p > 0.05$) (Figure 2A middle).

3.1.3 ITI Drift

The linear drift was normally distributed for 7 of our 8 variables ($p > 0.1$). The ANOVA didn't show any statistical difference between the four conditions ($F(3,29) = 1.047$, $p > 0.05$) (Figure 2A right).

3.2 Mono-fractal properties of tapping series

The mono-fractal exponent α was normally distributed for 7 of our 8 variables ($p > 0.1$). The grand average α between the 4 groups was 0.70 (± 0.13). The ANOVA didn't show any statistical difference between groups ($F(3,29) = 0.428$, $p > 0.05$) (Figure 2B left).

3.3 Multi-fractal properties of tapping series

The width of the multi-fractal analysis was normally distributed for 6 of our 8 variables ($p > 0.10$). The ANOVA show a statistical difference ($F(3,29) = 5.307$, $p = 0.005$). Post-hoc comparisons was significant ($p = 0.03$) between the control and the -2FBav group (Figure 2B right).

3.4 Deafferented participant

The t-test between – 3 FB group and IW showed significant differences for the mean ($t(7) = -14.98$, $p < 0.001$), the CV ($t(7) = -5.64$, $p < 0.001$), the drift ($t(7) = 3.71$, $p < 0.01$; Figure 2A), α-DFA ($t(7) = 7.06$, $p < 0.001$) and MF-Width ($t(7) = -10.22$, $p < 0.001$; Figure 2B).

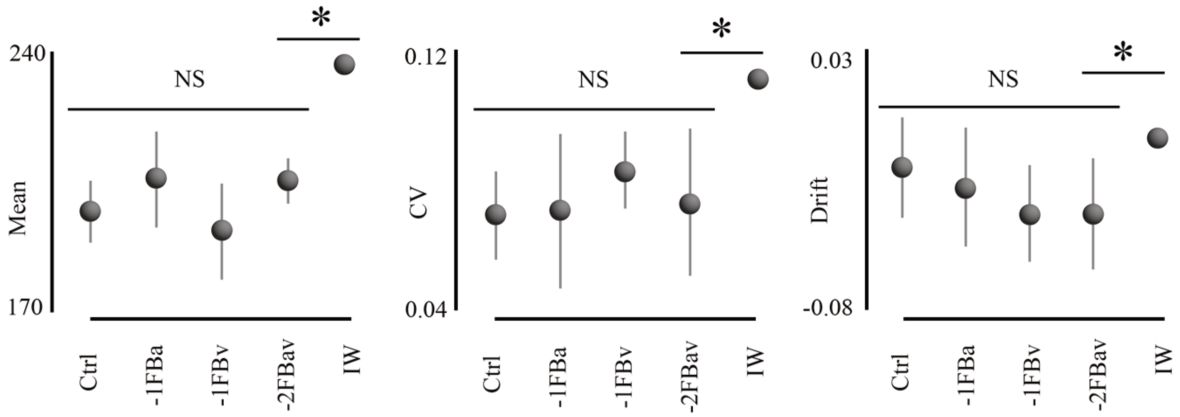

Figure 2A: Preliminary results of the tapping performance variables. The mean (left), the coefficient of variation (middle) and the drift (right) are statisticaly different between IW and group -2FBav. No statistical difference was found between groups Control (Ctrl), -1FBa, -1FBv and -2FBav. Vertical grey lines reflect the 95% confidance interval.

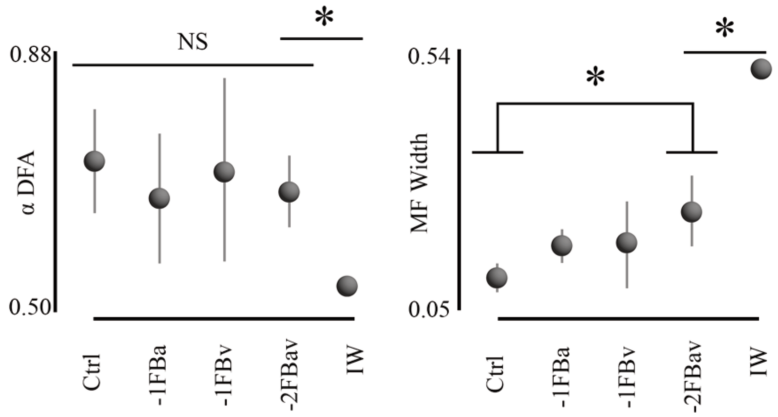

Figure 2B: Preliminary results of mono- and multi-fractal analysis. Both the mono-fractal exponent α and the width of the multi-fractal analysis present a statistical difference between IW and the -2Fav group. A statistical difference was highlited for the width of the MFDFA between the control group and the -2FBav group. Vertical grey lines reflect the 95% confidance interval.

4. Discussion

The present study was realized to clarify the functional significance of long-range correlations (namely the mono- and multi-fractal time series approach) in a behavioral task. We hypothesized first that mono-fractal exponent (α-DFA) should reflect the constraint imposed to the system and per se should co-vary with the level of performance. Specifically, we hypothesized a decrease of both variables with the loss of the proprioception. Secondly we hypothesized that the level of multi-fractality in inter-tap time series should evolve jointly with the number of configurations involved to perform the tapping task. In this sense, the MF-Width should increase with the number of feedback deprived from. After discussing the suitability and the limitation of our experimental protocol and design, we will highlight some considerations for the functional significance of both mono- and multi-fractal analysis.

4.1 Suitability of the experimental design

Effective adaptations, which composed in part the adaptability potential, could be defined as the capacity as long as possible to maintain a same level of performance despite increased constraints. The experimental design developed in this study was used to induce an increased level of constraints on the system without deteriorating the global performance. We used a simple synchronization-continuation finger-tapping paradigm as previous literature showed that the feedback deprivation (auditory and visual) should not alter classic motor performance (mean, CV and drift; Aschersleben & Prinz, 1997, 1995). Furthermore, the task performed easily and risk free for participants allowed us to combine a growing number of feedback deprivation, namely -1 FB, -2 FB and – 3FB. Has the distinction of many other tasks, the finger tapping enable a limited implication of biomechanical, external or cognitive constraints. In the present study, preliminary statistical analysis does not show an altered level of performance for the mean, the CV and the drift between all our groups of feedback deprivation (namely -1FBa, -1FBv and -2FBav). As previous literature generally considered only one feedback at a time, a possibility that presents itself quickly is that the performance may be dependent on a threshold of feedback number deprivation. Nevertheless, we previously published a study using quite similar experimental protocol and we didn't show any difference for the 2 variables discussed below (with the addition of the removal of

tactile feedback, see the following study in the Chapter 3 of this dissertation).

4.2 Deterioration of tapping performance

Proprioceptive feedback is essential in most everyday life, even the simplest motor task. In our study we additionally included 48 participants and one deafferented participant that allowed us to test the suitability of our experiment as the proprioception was showed to deteriorate the performance in multiple motor task and specifically in simple finger tapping task (Aschersleben & Prinz, 1997; Repp, 2013; Sarlegna et al., 2006; Rothwell et al., 1982). Our preliminary results highlight a clear distinction between IW and the –2FBav group for our three variables of performance. As the same metronome frequency was proposed, IW show a clear increase in the mean ITI, the coefficient of variation and the drift. However we need discuss some limitations regarding the results obtained by this participant. To confirm our results that the performance is only altered with proprioception deprivation, the upcoming analysis of participants who have undergone anesthetic block will allow us to better understand the importance of this sensory modality in performing a finger-tapping task in synchronization continuation. This approach seems interesting because it would allow to include healthy young participants without any kind of pathology and matched age that is not the case for IW compared to other groups (55 years old and 23.8 ± 5.6 respectively).

4.3 Mono-fractal properties reflect system adaptability

From the point of view of the current state of the art and the the loss of complexity with age or disease theory, the loss of complexity observed for IW could at first seem to reinforce the idea that mono-fractal analyzes can discriminate between variables generated by subjects with pathology (here IW) and healthy subjects (Goldberger et al., 2002; Lipsitz, 2002; Vaillancourt & Newell 2002). On the other hand, our results didn't show any significant differences between the 4 experimental groups. This result is not in agreement with the hypothesis of the loss of complexity due to the increased involvement of feedbacks to perform a task (e.g. Dingwell & Cusumano, 2010; Slifkin & Eder, 2014; Terrier et al., 2012; Warlop et al., 2013). According to these studies, we should observe a significant increase in complexity with the progressive deprivation of the number of feedbacks (mono- exponant α tending towards 1, pink noise). One possible explanation could be seen as the experimental protocol proposed

in our study. In this experiment, we directly manipulated the sensorial modalities (feedbacks) involved in the tapping task (visual and/or auditory) what was not the case in others studies which manipulate feedback indirectly (e.g. distance of the target task, free vs synchronized walk). These experimental conditions was supposed to induce an increased feedback loop like with an auditory metronome, therefore, contrary to our study, these manipulations do not make it possible to conclude in an unambiguous way on the effect which concerns the feedbacks involved in a task or the constraint imposed by the experimenter (e.g. difficulty of the task, double task paradigm). Our results therefore suggest that the complexity appreciated through the monofractal properties (DFA) of a time series accounts for the adaptability of the system. To confirm this result a step forward should be the analysis of the proprioception deprivation conditions by anesthetic block suppressing the sensory afference without affecting the motor control. The effect of the constraint imposed by the loss of proprioception should highlight that the mono-fractal exponant reflects the high constraint imposed to the participant and not directly the internal pathology of a system as IW.

4.4 Multi-fractal properties reflect the effective adaptation of the system

We hypothesized in our study that the multi-fractal properties (MF-Width) should evolve with all the number of feedback deprived from, regardless of whether they constitute a constraint (proprioception) or not (auditory, visual feedbacks). However, the state of the art did not allow us to specify the hypothesis concerning the meaning of this evolution, namely an increase or a decrease in the level of multi-fractality with the number of feedbacks. Our results showed a significant effect of the number of feedbacks deprived (with differences between control group and -2FBav group and IW). Moreover Figure 2B shows, a tendency for an increase between the suppressed numbers of feedback conditions. This pattern of results is therefore in line with the hypothesis that the level of multi-fractality reflects the possible configurations for carrying out the task, regardless of whether or not they are related to a constraint. Specifically our results show that the level of multi-fractality increases with the number of deleted feedbacks. This increase suggests that in response to increased deprivation of number of feedback, the ITI series produced have the properties of greater intermittency. The system transiently exploits different configurations, available

to perform the requested task at the same performance level (Ihlen & Vereijken, 2010). Referring to the concept of degeneracy, this refers to the degree of degeneracy, which can be defined as the number of "necessary and sufficient" configurations (Friston & Price, 2011) for performing a given function.

Nevertheless, it may seem counterintuitive that by depriving the system of an increasing number of feedbacks, the configurations / strategies used to the task increase. This result leads us to suggest that there is possible distinction between the number of alternative configurations available and the number of configurations that are actually used to perform the task. This distinction could be understood as the distinction between adaptability and effective adaptation. Adaptability refers to the freedom or potential of a system to adapt to changing circumstances, and effective adaptation refers to the processes implemented (or observed during the task), a certain level of both being necessary for the viability of a complex system. However, from the point of view of brain connectivity approach in the literature, the level of adaptability is directly related to the level of connectivity of the system, the number of possible functional interactions between different components (or areas). Thus, the quantitative measures of this connectivity are supposed to reflect the adaptability potential of the system (Ulanowicz, 2002).

Finally, the increase in the level of multi-fractality with the number of feedbacks deprived leads to questioning the conclusions of the literature more specific to tapping tasks. Indeed, based on tapping performance variables (accuracy, variability), much of the literature has converged on the idea that visual, auditory, and tactile feedback is not involved in synchronization continuation tapping tasks. However, deprivation of these feedbacks influences the level of multi-fractality of ITI products. From this point of view, we can consider that although a particular feedback may not be essential for maintaining the tapping performance, it nevertheless appears to be involved: its suppression seems to induce a more intermittent dynamics of the system, with a more transient exploitation of a larger number of alternative configurations that would compensate for the feedback suppressed. Thus, the more feedbacks that are suppressed, the more the system has to exploit a large number of alternative functional solutions to maintain the same level of performance in the task.

4.5 Conclusion

The results of this study indicate that the complexity extracted through the mono-

fractal properties of the inter-tap intervals in a synchronization continuation finger tapping task reflects the adaptability of the system, whereas the multi-fractal properties reflect the structure-function relationships of the system, such as the more or less transitory exploitation of different configurations or alternative strategies available for carrying out the task. These present results are significant in two respects, and open the way for work in this direction.

On the one hand, if the mono-fractal properties reflect a level of constraint imposed on the system, then this opens new questions to determine the relevance of mono-fractal properties as a marker of the "potential" of a system in a given task beyond their discriminating power between groups of pathological subjects vs healthy, young vs elderly subjects, etc. Indeed, depending on the intrinsic resources of a system in a particular task, the same difficulty level of the task will represent a different operating stress at the individual level.

On the other hand, most of the literature, which has simultaneously investigated mono- and multifractal properties has so far considered the level of multifractality to be a more sensitive and discriminating measure than the mono-fractal exponent and fundamentally equivalent in terms of functional significance, particularly in terms of complexity and loss of complexity, with age and disease (Dutta et al., 2012; Ivanov et al., 1999; Muñoz-Diosdado, 2005). Our study is, to our knowledge, the first to provide a clear demonstration that mono- and multi-fractal properties evolve independently and refer to distinct functional characteristics of the system. This opens up new research perspectives, particularly on the link between the multi-fractal properties observed at the level of behavioral variables in a given task, and simultaneous neuronal connectivity measurements with neuroimaging methods.

Acknowledgements

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Conflict of interest

The authors declare no conflicts of interest, financial or otherwise.

1st Transition

From behavioral dynamics to brain networks dynamics

Our first study investigated the functional meaning of mono- and multi-fractal analysis in a finger-tapping task under various conditions of feedback privation to test the effective adaptation of the subjects (Figure 2C). As expected, our first (preliminary) results highlight a possible distinction into the functional meaning of mono- and multi-fractal analyzes performed during a prolonged finger-tapping task. The fact that the mono-fractal exponent and the width of the multi-fractal spectra do not covariate according to the number of sensory feedbacks deprived leads us to consider that the two analyzes would not reflect the same information. On one hand, mono-fractal exponent could indicate the loss of adaptability potential without allowing discriminating between a loss of adaptability due to the proprioception deprivation or neurological impairment (IW, deafferented participant, 59 years old). On the other hand, multi-fractal properties could reflect the effective adaptation to a prolonged sensorimotor task. Such capacity could be seen as a robustness property of the system and be part of an intermittent functioning (degenerate properties). The suppression of feedbacks in carrying out the task would cause a temporary "disruption" of the system. To continue to perform the task while maintaining an identical level of performance output, the system would try to find compensatory strategies, especially in the different brain networks available. The results obtained in this first study open up a way for future research aiming to investigate the potential link between the degenerate properties (and intermittence property) at the brain level with multi-fractal properties at the behavioral level.

In the following study, we decided to investigate this question using the same simple finger-tapping task. For that purpose, dynamic functional connectivity analysis of some relevant brain areas monitored by functional near-infrared spectroscopy (fNIRS) was undertaken (see box 2 for an introduction of the fNIRS neuroimaging method). Then the possible links between the multi-fractal spectrum width (MF-Width) and the degenerate properties of the involvement of the prefrontal and motor cortices were investigated when multiple numbers of feedbacks were deprived (-1FB, -2FB and -3FB). The study 2 tests the following hypothesis when considering the functional significance of multi-fractal analyzes: if the width of the spectrum actually reflects a greater intermittence of operation of the underlying system, the number of brain networks involved in performing the sensorimotor task should covariate.

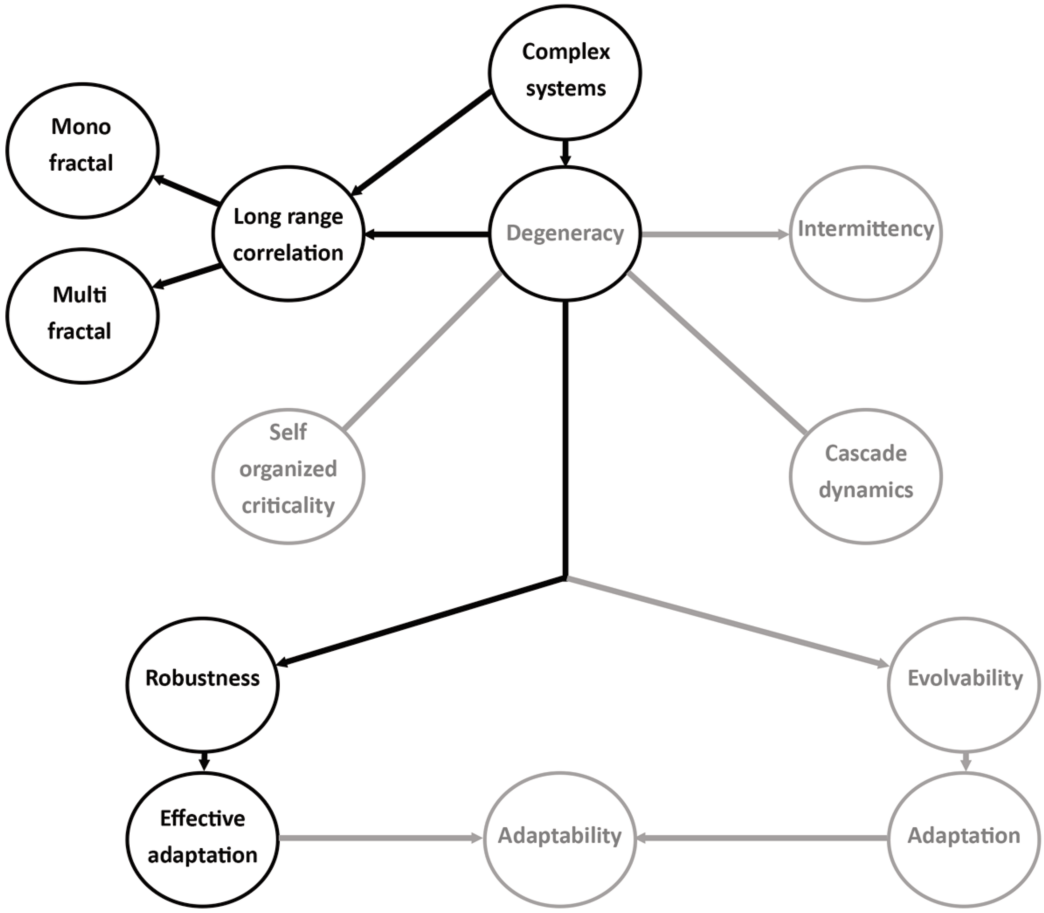

Figure 2C: Diagram representing the different keywords investigated and discussed during the first study (in black). A complex system approach allows for testing the effective adaptation of healthy subjects and one deafferented subject under various sensory modalities during a finger-tapping task. Mono-fractal and multi-fractal analysis present separated results in healthy subjects.

Box 2

Near-Infrared Spectroscopy

"On December 28, 1976 our family menu featured a grilled chuck roast, the poor academic's substitute for steak. This very American cut of beef still contains part of the shoulder blade of the steer; a flat piece of bone perhaps 3 or 4 mm thick, about the same as the human skull. I asked my 14 yr old son Paul to clean all the muscle tissue from the bone. When he had done so we held the pink object up against the light and noticed that the shadow of a finger could easily be noted in the diffuse red light coming through the bone."

(Jöbsis-vander Vliet, 1999)

Let us first for the non-familiar reader/user with fNIRS to introduce briefly this neuroimaging method. Functional Near-Infrared spectroscopy (fNIRS) allows for investigating the brain activity in multiple cognitive or motor tasks and with a high range of populations: from baby to pathological subjects. fNIRS is often considered to be a relatively young neuroimaging method (which is not so true, when compared to other methods such as fMRI or EEG for example). In fact, it was in 1831 that Bright discovered transparency of human tissues properties. This phenomenon, discovered thanks to a simple candle allowed highlighting what is called the "transillumination" phenomenon. Nevertheless, it took about 150 years for the necessary technological developments to allow Jöbsis (Jöbsis, 1977) to

publish its first work on the development of a tool/device for the extraction of cerebral hemodynamics parameters (for a review of these discovery see Piantadosi, 2007). The first applications and publications will reach the scientific community only a few years later in the 80's by the team of Marco Ferrari (see Ferrari & Quaresima, 2012 for a review). It follows as often with promising new methods a rapid development of tools and instrumentation that are still growing up today. Currently, the most common fNIRS device on the market is based on the so-called continuous wave (CW) instrumentation. The physical principle and physiological explanations of this method could be found in two previous dissertations of our lab (Mandrick, 2013; Besson, 2017) and in multiple dedicated scientific papers (Quaresima et al., 2012; Quaresima & Ferrari, 2016; Perrey, 2008, 2014; Scholkmann et al., 2014). Briefly as its name suggests, CW fNIRS will emit a light source continuously, at least two (more for some devices) separate wavelengths in the near-infrared spectral window. A receiver placed in most cases 3 cm from the source will collect the light passing through the biological tissues. The detected light is assumed to have reached a depth of approximately half the interoptode (emitter-receiver) distance. The use of two distinct wavelengths will make it possible to relatively quantify the changes in oxygenated hemoglobin (O_2Hb) and deoxygenated hemoglobin (HHb) (Figure 2D).

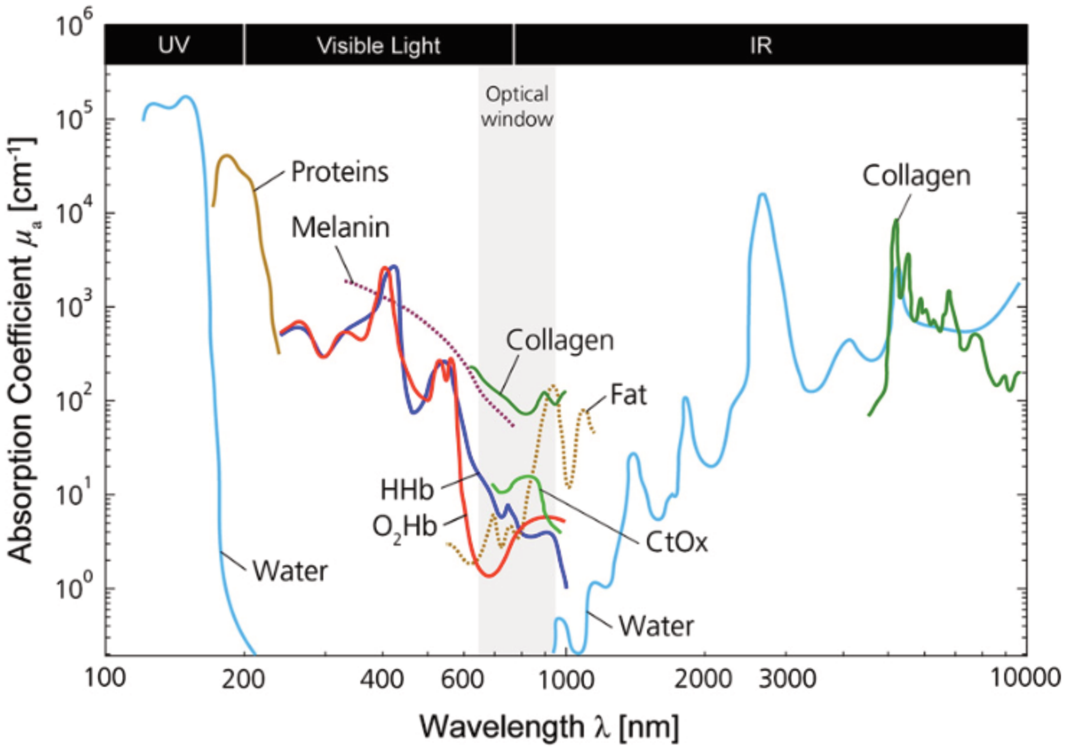

Figure 2D: Absorption spectra for chromophores present in the human body. The absorption spectrum of hemoglobin depends on its oxygentation state. The near infrared optical window (in grey) of interest to monitor O_2Hb and HHb is located between wavelengths of 690 nm to 950 nm (Strangmann et al., 2003).

One of the main limitations of fNIRS is its spatial resolution. Indeed this technique based on the luminous emition thanks to optical fibers or electroluminescent diodes allows only reaching the surface of the cortex and not to the subcortical structures. Although the literature generally considers that the photons travel a banana-shaped path through the brain, the recent tools make it possible to simulate the spatial sensitivity of the fNIRS as illustrated in the example plot (Figure 2E). The exponential development of computers capabilities and so-called “open access big data” also allows for the research field based on the fNIRS to be in perpetual evolution. Currently when writing the present dissertation, the development of tools such as the Atlas Viewer toolbox (Aasted et al., 2015) based on Monte-Carlo simulations currently makes it possible to estimate the propagation of photons relatively accurately and thus to approach more realistic cortical

areas investigated when using fNIRS.

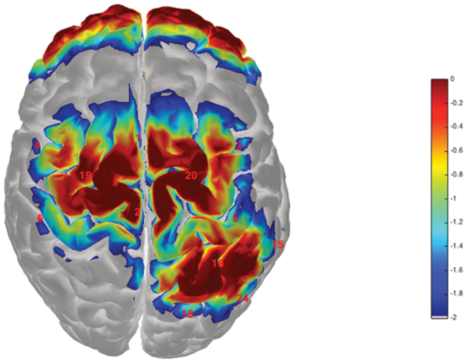

Figure 2E: Example of the use of the Atlas Viewer toolbox to simulate photon propagation. Unlike some manuscripts generally considering a unique measurement point of brain activity between emitter and receiver in fNIRS, monte carlo simulation highlights a larger area which should be considered in the analysis of fNIRS time series. Both O_2Hb and HHb signals are generally composed of multiple cortical areas contributions. Colorbar reflect the sensitivity logarithmically of the brain surface depending of optodes position (red = highly sensitive and bleu = low sensitivity). The brain is oriented with the prefrontal cortex upwards.

In addition, the positioning of optodes relative to anatomical regions well defined by MRI is greatly facilitated by using toolboxes such as NIRS-SPM (Ye et al., 2009; NFRI function by Singh et al., 2005), HomER (Huppert et al., 2009) and fNIRS Optodes' Location Decider (Morais et al., 2018). It allows getting the reproducibility between studies.

fNIRS studies trying to investigate brain function have based their analyzes on previous methods developed in fMRI as both neuroimaging methods measure indirectly the brain activation based on the neurovascular coupling phenomenon. Furthermore, fNIRS was shown as a reliable method (compared to fMRI) to provide relevant metrics by using multiple paradigms in humans: for instance, evoked-activation patterns during cognitive tasks (Cui et al., 2011), resting state functional connectivity (Duan et al., 2012) and effective connectivity during a motor tapping task (Anwar

et al., 2016).

To date, and in concern with our main hypothesis, the most commonly used strategy for examining dynamic functional connectivity has been a sliding window Pearson's correlation approach (Chang and Glover, 2010; Hutchison et al., 2013a, 2013b; Sakoglu et al., 2010). Although this analysis has certain limitations (Hutchinson et al., 2013; Leonardi & Van De Ville, 2015; Hidrinks et al., 2016; Shakil et al., 2016), it is generally used (sometimes as a first investigative analyzes) because of being both easily understandable and computationally inexpensive. Combined with appropriate preprocessing and classification analysis of the time series, fNIRS could reveal interesting properties of the brain combined with multiple motor tasks and in our case, can reflect the number of cortical brain networks involved in a continuous motor task.

Chapter 3

Concurrent changes of brain functional connectivity and motor variability when adapting to task constraints

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Abstract:

In behavioral neuroscience, the adaptability of humans facing different constraints has been addressed on one side at the brain level, where a variety of functional networks dynamically support the same performance, and on the other side at the behavioral level, where fractal properties in sensorimotor variables have been considered as a hallmark of adaptability. To bridge the gap between the two levels of observation, we have jointly investigated the changes of network connectivity in the sensorimotor cortex assessed by modularity analysis and the properties of motor variability assessed by multi-fractal analysis during a prolonged tapping task. Four groups of participants had to produce the same tapping performance while being deprived from 0, 1, 2, or 3 sensory feedbacks simultaneously (auditory and/or visual and/or tactile). Whereas tapping performance was not statistically different across groups, the number of brain networks involved and the degree of multi-fractality of the inter-tap interval series were significantly correlated, increasing as a function of feedback deprivation. Our findings provide first evidence that concomitant changes in brain modularity and multi-fractal properties characterize adaptations underlying unchanged performance. We discuss implications of our findings with respect to the degeneracy properties of complex systems, and the entanglement of adaptability and effective adaptation.

Keywords: adaptability, fNIRS, modularity, fractal properties, tapping

1. Introduction

The huge ability of the brain to exploit its inherent plasticity to adapt to intrinsic or extrinsic constraints over different time scales is stunning and vital (Bassett et al., 2011; Fallani et al., 2014). Depending on circumstances, adaptability may take the form of robustness against changing conditions as well as the form of innovation and evolvability (Whitacre, 2010; Whitacre and Bender, 2010). In a complementary way the brain allows for preserving a given cognitive-motor performance in the face of tumor growth and resection (Duffau, 2014) as well as diversifying the repertoire of our cognitive-motor behaviors with learning, for example (Bassett et al., 2011; Dayan and Cohen, 2011). While some studies has focused on the precise neuro-physiological mechanisms sustaining the brain's capacity to adapt, others have provided insight into more generic organization principles inherent in complex systems, notably through the assessment of brain network connectivity (e.g., Tononi et al., 1994; McIntosh et al., 1999; Sporns, 2012; Tognoli and Kelso, 2014). From this latter perspective, the brain's functional organization has been conceived as a dynamic balance between functional segregation and integration of subparts of the entire network (Friston, 1994; Tononi et al., 1994; Sporns, 2013). At a given observation scale, the brain network can thus be assessed as a modular organization, modules being defined as clusters that are densely connected within but weakly connected between them (Bullmore et al., 2009; Bassett and Gazzaniga, 2011; Sporns and Betzel, 2016). Moreover, complexity is increased by the dynamic properties of the functional connections within and between modules, which may compose and recompose depending on circumstances. In particular, such connectivity scheme is closely related to degeneracy, a key property characterizing the structure-function relationship in the brain (Tononi et al., 1999; Noppeney et al., 2004). Degeneracy refers to a many- to-one structure-function relationship, with a partial functional overlapping between modules of the network: different parts may perform the same function or specialized functions under circumstances (Edelman and Gally, 2001; Price and Friston, 2002; Whitacre and Bender, 2010). Together, the modular and degenerate properties of network connectivity constitute an essential basis for adaptability, supporting robustness and adaptive changes facing various conditions (Jirsa et al., 2010; Whitacre, 2010; Bassett and Gazzaniga, 2011; Grefkes and Ward, 2014). The variety of the dynamical states or network configurations involved to

maintain a given function or performance, whether at rest (Deco et al., 2011) or during a task may thus basically reflect adaptation to changing conditions.

Developing in parallel in a bio-behavioral literature, a significant amount of research focusing on the temporal dynamics of diverse macroscale variables (e.g., heartbeat intervals, Ivanov et al., 2001; force production, Athreya et al., 2012; gait and coordination dynamics, Hausdorff et al., 1996; inter-tapping intervals, Torre and Delignières, 2008) has considered that fractal fluctuations are the hallmark of underlying dynamic complexity and system's adaptability (Ivanov et al., 1998; Gilden, 2001; Ashkenazy et al., 2002; Kello et al., 2010; Manor et al., 2010; Torre and Balasubramaniam, 2011; Delignières and Marmelat, 2013). Notably, a breakdown of the fractal properties in pathological and/or elderly compared to young and healthy subjects has been evidenced repeatedly, supporting the idea that loss of fractal properties can be considered a marker of the general loss of adaptability coming along with aging and disease (Goldberger, 1996; Hausdorff et al., 1996; Peng et al., 2000; Blaszczyk and Klonowski, 2001; Lipsitz, 2002). In particular, in the context of neurological disorders such as Parkinson, Huntington or Alzheimer diseases, research programs have been assessing the diagnostic and/or prognostic (Mäkikallio et al., 2001; Goldberger et al., 2002; Hu et al., 2009) power of fractal properties in sensorimotor variables. Thereby studies have made implicit but strong assumptions on a close relationship between network alterations at the brain level and fractal properties at the effector level. In a complementary vein, the fractal properties of motor variables have been shown sensitive to experimental restriction/augmentation of the sensorial feedbacks available to subject's performance on given tasks (Slifkin and Newell, 1999; Manor et al., 2010; Athreya et al., 2012; Warlop et al., 2013). Finally, the literature has evidenced that fractal properties may be variable within a same time series (multi-fractal series). Different fractal scaling regimes may apply in an intermittent way to different windows of observation within the series, thus reflecting variations in the system's underlying dynamic organization and exploration of new solutions (e.g., Ivanov et al., 2001, 2004; Nunes Amaral et al., 2001; Hu et al., 2004; Stephen and Anastas, 2011; Dixon et al., 2012; Dutta et al., 2013). In fact, where comparison of the Gaussian properties of any variable of interest may indicate unchanged output across groups or experimental conditions, alterations of its fractal properties often reflect underlying reorganizations in the

performing system. To our knowledge, however, the question of whether/to what extent the multiple connectivity patterns forming and reforming in the brain directly spill over into the behavioral outcome remains largely unanswered so far: When the brain adapts facing changing conditions to sustain steady motor-behavioral performance, are the *ad hoc* reorganizations in network connectivity reflected in some distinctive fractal properties of behavioral variability?

In view of the above literature, the degeneracy or intermittency of functional brain networks may be reflected in the multi-fractal properties at the behavioral level. Imposing constraints by manipulating the feedbacks available to perform a motor task is likely to alter the expression of degeneracy in the motor output. Therefore, the purpose of the study was to bridge levels of observation to establish a direct relationship between degenerate connectivity patterns enabling adaptation at the brain level, and fractal properties as their dynamic signature in the sensorimotor outcome. Herein we consider adaptability as the capacity to maintain a given function or performance despite changing constraints. Thus, a heuristic experimental paradigm should allow us to manipulate the experimental constraints imposed to subjects in a given task without these manipulations affecting their performance, by virtue of the system's capacity to adapt. In this way, we should be able to assess jointly the variety of patterns of brain connectivity that are involved intermittently during task performance, and the dynamic fractal properties of the task variable. Therefore, we used the well-known finger-tapping paradigm (Wing and Kristofferson, 1973), where previous literature has showed that experimental deprivations of visual, auditory, or tactile feedbacks are not such as to alter tapping performance (Aschersleben and Prinz, 1995, 1997; Stenneken et al., 2006; Repp and Su, 2013). Following from the above, we hypothesized that the variety and intermittency of brain networks (degeneracy) involved in the task and the dynamical fractal properties of tapping series would evolve jointly as a function of different conditions of feedback deprivation, while tapping performance should stay invariant.

2. Materials and methods

Participants

Thirty-two healthy volunteers took part in the study (9 women, 23 men, 26.9 ± 6.3 years of age). All participants signed a written informed consent before participating in the study. All participants

were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971) and reported normal hearing and normal or corrected vision. None showed any sign of neurological disease, nor reported extensive practice in music. All procedures were approved by the local ethics committee (IRB- EM: 1610C, Montpellier). All participants gave written informed consent in accordance with the Declaration of Helsinki for human experimentation.

Experimental Design and Procedure

The experimental design was an independent-group design, with the experimental factor being the numbers of sensorial feedbacks the participants were deprived from. Participants were randomized to one of the four following conditions: (i) no feedback deprivation (Control), (ii) deprivation of one feedback, either visual, or auditory, or tactile (-1 FB); (iii) simultaneous deprivation of two feedbacks, either visual and auditory, or visual and tactile, or auditory and tactile (-2 FB); (iv) simultaneous deprivation of three feedbacks, visual, auditory and tactile (-3 FB). Participants were deprived of visual and auditory feedbacks using a sleeping mask and ear defenders, respectively. The tactile feedback was prevented by the means of a removable striking surface at the place where the index finger tapped ("air tapping" e.g., Aschersleben and Prinz, 1997). Each participant performed three tapping trials in the assigned conditions. As mentioned above, none of the visual, auditory or tactile deprivations should alter tapping performance (Aschersleben and Prinz, 1995, 1997; Repp and Su, 2013), and no study to our knowledge conveys strong assumptions about any differential effect of these conditions on the temporal structure of tapping. Nevertheless, rather than arbitrarily removing one of the three feedbacks for each participant or for a whole group, participants of the −1 FB group performed one trial in each of the visual, auditory and tactile feedback deprivation conditions in a random order. Likewise, participants of the −2 FB group performed one trial in each of the visual-auditory, visual-tactile, and auditory-tactile deprivation conditions in a random order. Participants of the Control and −3 FB groups performed three times the same.

The Tapping Task

The experiment was conducted in a quiet room. Participants were sitting comfortably on an adjustable chair, with their dominant side forearm and palm of the hand resting on a customized plinth (570 × 160 × 50mm) on a table in front of them. Subjects realized a tapping task according to a conventional

synchronization-continuation paradigm (Wing and Kristofferson, 1973; Vergotte et al., 2017): during the initial synchronization phase, the tempo was prescribed by a PC- driven auditory metronome delivering 20 signals at a frequency of 1.5 Hz (0.666 s inter-tap intervals), known as a comfortable tapping frequency (Fraisse, 1966; Torre and Delignières, 2008). Once the metronome stopped, participants had to continue tapping by maintaining the prescribed tempo as accurately and regularly as possible for the whole trial duration. The duration of each trial was set to 6min 40s so as to ensure a sufficient number of inter-tap intervals to be submitted to subsequent fractal analysis (Delignieres et al., 2006; Eke et al., 2012). Between each of the three trials, participants had a 2-min rest.

Data Collection

Tapping Performance

Movements of the index finger were captured using a single-axis accelerometer (15 × 15 mm) fixed on the nail so as to minimize possible device-induced sensorial feedbacks. Acceleration data were collected using a Labjack U12 device and stored via its software (LJStream v1.07). The sampling rate was 300 Hz.

Functional Near-Infrared Spectroscopy Measurements

Hemodynamic changes in the cortex during the tapping tasks were measured by two synchronized continuous waves (CW) multi-channel functional near infrared spectroscopy (fNIRS) devices (Oxymon MkIII and Octamon, Artinis Medical Systems, The Netherlands) with a sampling rate of 10Hz. fNIRS is an optical method using near-infrared light to measure relative changes of oxyhemoglobin (O_2 Hb) and deoxyhemoglobin (HHb) in the cortex (Scholkmann et al., 2014). In the present study, a customized cap was used to place beside the vertex (Cz) a 16-channels array on three regions of interest [premotor cortex (PMC), primary motor cortex (M1) and supplementary motor cortex (SMA)] on both hemispheres. Another 8-channel array was placed on the prefrontal cortex [PFC, Nazion (Nz) was the reference point]. Due to different sensibility of light penetration among brain regions using fNIRS (Brigadoi and Cooper, 2015), the inter-probe distance was fixed at 30 mm for M1, PMC and SMA, and 35 mm for PFC. After positioning all we used a 3D-digitizer (Fastrack, Polhemus, United States) to collect the location of each probe for each subject. NFRI function (Singh et al., 2005) included in the NIRS-SPM toolbox (Ye et al., 2009) was used to

extract the Montreal Neurological Institute coordinates (MNI). The positioning of the 24 channels (MNI coordinates and Brodmann area correspondences) can be seen in Figure 3A**.**

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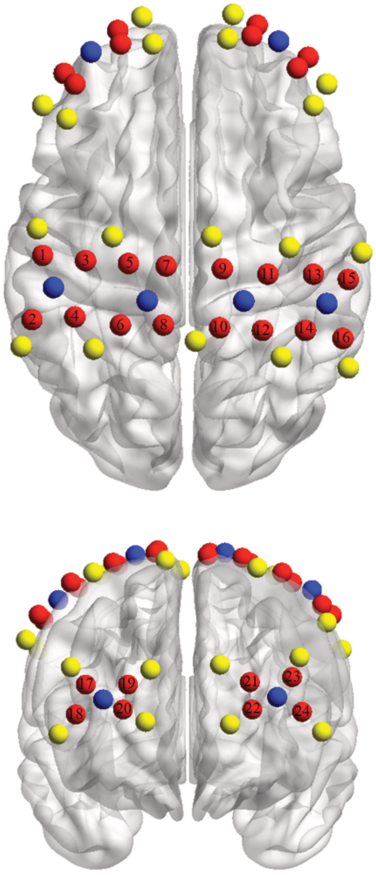
A)



B)

	MNI (x,y,z)			BA (%)
Ch 1	-54	-17	58	4 - Primary Motor Cortex (15) 6 - Pre-Motor and Supplementary Motor Cortex (85)
Ch 2	-58	-41	54	1-2-3 - Primary Somatosensory Cortex (86) 4 - Primary Motor Cortex (8) 40 - Supramarginal gyrus part of Wernicke's area (6)
Ch 3	-38	-19	71	4 - Primary Motor Cortex (2) 6 - Pre-Motor and Supplementary Motor Cortex (98)
Ch 4	-42	-40	67	3 - Primary Somatosensory Cortex (31) 4 - Primary Motor Cortex (63) 6 - Pre-Motor and Supplementary Motor Cortex (6)
Ch 5	-22	-20	77	6 - Pre-Motor and Supplementary Motor Cortex (100)
Ch 6	-25	-43	75	4 - Primary Motor Cortex (41) 6 - Pre-Motor and Supplementary Motor Cortex (59)
Ch 7	-8	-21	78	6 - Pre-Motor and Supplementary Motor Cortex (100)
Ch 8	-9	-43	79	4 - Primary Motor Cortex (61) 6 - Pre-Motor and Supplementary Motor Cortex (39)
Ch 9	13	-22	79	6 - Pre-Motor and Supplementary Motor Cortex (100)
Ch 10	12	-44	80	4 - Primary Motor Cortex (78) 6 - Pre-Motor and Supplementary Motor Cortex (22)
Ch 11	30	-24	75	6 - Pre-Motor and Supplementary Motor Cortex (100)
Ch 12	28	-45	74	4 - Primary Motor Cortex (49) 6 - Pre-Motor and Supplementary Motor Cortex (51)
Ch 13	47	-24	67	4 - Primary Motor Cortex (10) 6 - Pre-Motor and Supplementary Motor Cortex (90)
Ch 14	44	-45	65	3 - Primary Somatosensory Cortex (8) 4 - Primary Motor Cortex, (71) 6 - Pre-Motor and Supplementary Motor Cortex (20)
Ch 15	60	-26	54	4 - Primary Motor Cortex (46) 6 - Pre-Motor and Supplementary Motor Cortex (54)
Ch 16	58	-48	52	1-2-3 - Primary Somatosensory Cortex (97) 40 - Supramarginal gyrus part of Wernicke's area (3)
Ch 17	41	53	26	45 - pars triangularis Broca's area (17) 46 - Dorsolateral prefrontal cortex (83)
Ch 18	45	57	14	10 - Frontopolar area (21) 46 - Dorsolateral prefrontal cortex (79)
Ch 19	24	65	26	9-46 - Dorsolateral prefrontal cortex (27) 10 - Frontopolar area (73)
Ch 20	26	69	16	10 - Frontopolar area (100)
Ch 21	-25	62	27	9-46 - Dorsolateral prefrontal cortex (52) 10 - Frontopolar area (48)
Ch 22	-26	67	16	10 - Frontopolar area (90) 46 - Dorsolateral prefrontal cortex (10)
Ch 23	-42	47	29	45 - pars triangularis Broca's area (41) 46 - Dorsolateral prefrontal cortex (59)
Ch 24	-46	51	15	45 - pars triangularis Broca's area (30) 46 - Dorsolateral prefrontal cortex (70)

Figure 3A: Localization of fNIRS probes, channels, MNI coordinates and Brodmann correspondences. **(A)** Yellow: transmitters, blue: detectors and red: channels. **(B)** MNI coordinates for each channel (n = 24) with x, y, and z coordinates. On the right, Brodmann area correspondence (number, name and %) extracted from the NIRS-SPM toolbox (NFRI function).

Data Analysis

Motor Variability Analysis

Preprocessing of tapping data

Raw acceleration data were first low-pass filtered using a Butterworth zero-phase digital filter (Frequency = 15 Hz). Then, a MATLAB in-house script (MATLAB 2014b, The MathWorks) for peak detection was used to extract the onsets of the subsequent finger taps. Series of inter-tap intervals (ITI) were then computed as the differences between subsequent tap times. For each trial, the first twenty ITI (corresponding to the synchronization phase) were discarded, and series of 512 ITI in the continuation phase were retained for further analyses. For each ITI series, we computed the typical performance variables used in tapping studies (Billon et al., 1996; Repp and Su, 2013), namely the mean, the coefficient of variation (CV) and the linear drift over the trial duration.

Characterizing fractal properties of inter-tap interval series

Fractal time series are basically characterized by fluctuations with scale invariant structure [i.e., obeying a power law distribution $X(ct) = c^{H}X(t)$, where X is the signal, c is a constant, H is the fractal exponent] and temporal long-range correlations (meaning the autocorrelation function of the time series decays as a power- law without falling to zero). To analyze the fractal properties of ITI series, we used the Multifractal Detrended Fluctuation Analysis (Ivanov et al., 1999; Kantelhardt et al., 2002; MFDFA, Ihlen, 2012). MFDFA is derived from the original Detrended Fluctuation Analysis (DFA), which estimates the mono-fractal properties of a time series (Peng et al., 1995). In short, DFA exploits the diffusion properties of the time series, analyzing the relationship between the average amplitude of fluctuations and the size of the observation window within which these fluctuations are measured. For fractal series, a power-relationship characterized by the mono-fractal exponent $\alpha \in [0, 2]$ is expected: in particular, for $\alpha = 0.5$ the series is white noise, for $\alpha = 1$, the series is so-called *1/f noise*, and for $0.5 < \alpha < 1$ the series is considered stationary and containing persistent long- range correlations. By yielding a single fractal exponent (α) characterizing the average fractal properties of a time series, the DFA assumes that the fractal properties are homogeneous over all scales of the entire time series.

However, instead of being characterized by a single homogeneous fractal exponent, time series of bio-behavioral variables are

often characterized by an inhomogeneous distribution of variability (intermittent fluctuations). The fractal exponent may vary over time scales: the series is actually characterized by multiple fractal exponents (Ihlen and Vereijken, 2010) and with this viewpoint the MFDFA was developed (Kantelhardt et al., 2002; Ihlen, 2012). Since we hypothesized that the system's adaptations to imposed task constraints would be expressed through the variety of fractal properties in ITI series, we opted for MFDFA analysis. MFDFA basically uses the same steps as DFA, but the average amplitude of the fluctuations is calculated using q^{th} order fluctuation function, with q varying from−10 to +10 in steps of 0.5, whereas DFA computes the amplitude of fluctuations only for $q = 2$. In brief, the time series *x(i)* is first integrated into *X(k)*, and divided into N_n adjacent segments of length n. Within each segment ($s = 1, \ldots, N_n$) the local trend is then subtracted from *X(k)*. So, the amplitude of fluctuations is computed for each detrended segment according to:

$$F^2(n,s) = \frac{1}{n} \sum_{k=(s-1)n+1}^{sn} \left[X(k) - X_{n,s}(k)\right]^2 \text{ (Eq.1)}$$

The variance is then averaged over all segments to obtain the q^{th} order fluctuation function:

$$F_q(n) = \left\{ \frac{1}{N_n} \sum_{s=1}^{N_n} \left[F^2(n,s)\right]^{q/2} \right\}^{1/q} \text{ (Eq.2)}$$

If the series *x(i)* presents fractal properties, the generalized Hurst exponent *h(q)* is given by:

$$F_q(n) \propto n^{h(q)} \text{ (Eq. 3)}$$

According to Kantelhardt et al. (2002), the result of MFDFA can then be converted into the classical multi-fractal formulation using simple transformations, to be finally summarized by the multi-fractal spectrum representing *F(α)* as a function of *α(q)*, where *F(α)* is the fractal dimension (or dimension of the subset of the series that is characterized by *α*), and *α* is the Hölder (or singularity) exponent (see Figure 3B). Our variable of interest is the width of the multi-fractal spectrum (MF-Width), meaning the range between the minimum and maximum exponents *α(q)* characterizing the time series, which represents the degree of multi-fractality. Figure 3B illustrates the distinction between mono- and multi-fractal properties of two experimental time series as assessed by DFA and MFDFA.

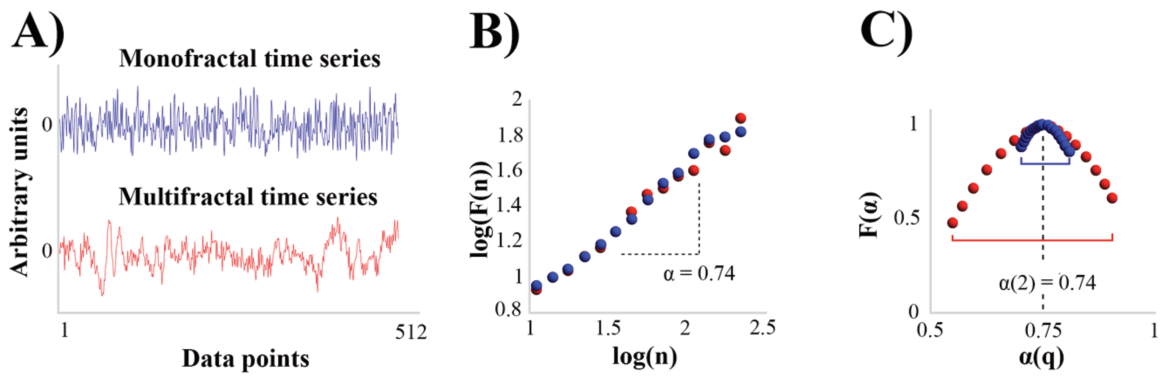


Figure 3B: Distinction between DFA and MFDFA analysis for mono- and multi-fractal time series. **(A)** Two experimental time series of 512 pts: in blue, the time series is closely mono-fractal; in red, the time series is multi-fractal. The Y-axis displays an arbitrary unit centered to zero. **(B)** Results yielded by DFA for the two time series. The plot shows the size of fluctuations *F(n)* as a function of the size *n* of observation windows in bi-logarithmic coordinates. The mono-fractal exponent α is given by the slope of log(*F(n)*) vs. log*(n)*. According to the plot, both time series present long-range correlations and are characterized by the same mono-fractal exponent (α = 0.74). **(C)** Multi-fractal spectra for the two time series. The right-hand side of the spectrum accounts for the influence of large-amplitude fluctuations (*q* positive), and the left-hand side accounts for the influence of low amplitude fluctuations (*q* negative). The width of the multi-fractal spectrum is then calculated by the difference $\alpha\,(q)max - \alpha\,(q)_{min}$. Comparison of plots **(B, C)** shows that while both time series present globally the same mono-fractal exponent, the blue series is close to mono-fractal whereas the red one is clearly multi-fractal.

2.5.2 Brain Connectivity Analysis

fNIRS preprocessing. A common approach as described in Huppert et al. (2009) was used to obtain O_2Hb and HHb concentration changes. We extracted 6min of raw (light intensity) data after the end of the metronome using the ARTINIS software (Oxysoft v3.0.95). Data were then uploaded in MATLAB. We first converted intensity data to optical density (OD). Then we applied the moving standard deviation and spline interpolation methods (SDThresh = 20, AMPThresh = 0.5, tMotion = 0.5 s, tMask = 2 s and p = 0.99; Scholkmann et al., 2010), combined with wavelet artifact correction (iqr = 0.1; Molavi and Dumont, 2012) as

recommended in Cooper et al. (2012) to remove possible head motion artifacts. To retrieve the relative concentration changes (expressed in μM) of O2Hb and HHb, we applied the modified Beer-Lambert law (Kocsis et al., 2006) on OD data, by including an age-dependent constant differential path length factor ($4.99 + 0.067 \times \text{Age}^{0.814}$). The presence of a strong cardiac oscillation (frequency peak around 1 Hz) in the power spectrum of O2Hb signal indicates a good contact between the optical probe and the scalp (Themelis et al., 2007). 6.25% of all channels analyzed did not satisfy this condition and were discarded. For subsequent analysis, a band pass zero-phase digital filter (4th order Butterworth, cut-off frequency [0.009 0.08]) was used to remove physiological noise like cardiac, respiratory, Mayer waves and very low frequencies (Scholkmann et al., 2014). A linear detrending was then used to remove possible slow drifts.

Functional connectivity analysis. In the line of assessing functional network connectivity free from the constraint of neuroanatomical a-priori assumptions, the most commonly used method is based on the bivariate Pearson's correlation analysis (Biswal et al., 1995): it consists in computing the statistical dependency between two or more time series to explore the influence that one region of interest exerts on others (seed based correlation analysis), or in computing all possible connections at the level of the entire brain (whole brain correlation analysis), at rest or during a task (Medvedev, 2014).

Then an $N \times N$ adjacency matrix was constructed, reflecting the strength of the correlation between each time series. However, different studies applying such analyses have implicitly considered that patterns of connectivity were stationary and computed an average matrix over the whole scanning period. Instead, to assess the dynamic functional connectivity (dFC) between the present 24 fNIRS channels, we used a sliding window correlation analysis as proposed in the literature (Hutchinson et al., 2013). For each subject, this method yielded a number *n* of matrices depending on the window size and a shift (in samples), summarizing the evolution of all connections between channels over time. As there is no consensus in the literature we used three widespread window sizes (30 s, 75 s and 120 s; Hutchinson et al., 2013) and a shift of 1 sample (100 ms). Figure 3C illustrates the pipeline for these analyses.

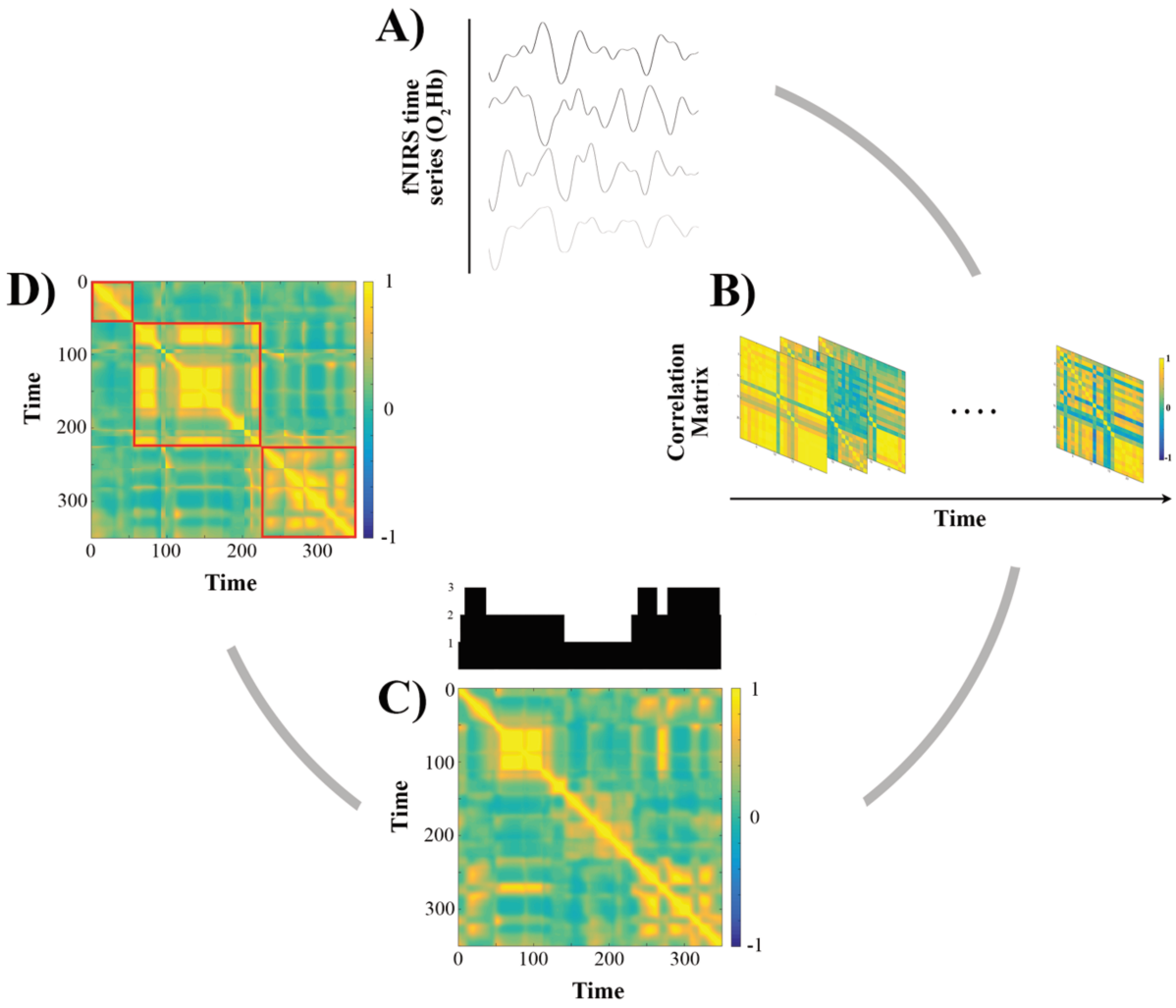


Figure 3C: Illustration of the functional connectivity analysis for one representative subject. **(A)** Extraction of O_2Hb fNIRS time series for all channels after preprocessing and band pass filtering (cut off frequency [0.08 0.009]). **(B)** Sliding window Pearson's correlation analysis for window sizes of 30, 75, and 120 s. **(C)** Grand average correlation analysis between each matrix. The upper plot shows communities detected for 360 s (3 communities in this example). **(D)** Grand average matrix after putting in the order of community. Red squares delimit each community.

Modularity analysis. Once obtained the time evolution for all connections, one of the main challenges in dFC analysis is to classify the multiple networks obtained with reliable metrics (Fallani et al., 2014). A network is a collection of nodes (vertices) and links (edges). All networks are represented mathematically through their connectivity (adjacency) matrices. Rows and columns correspond to nodes and entries denote links that are weighted. Based on the graph theory analysis, one of

the relevant methods to extract the number of different communities involved during the task is the modularity analysis (Rubinov & Sporns, 2010; Newman, 2006). Modularity quantifies the degree to which the network may be subdivided into delineated and no overlapping groups. In other words, modularity reflects strong links within each community and weaker links between communities. The Modularity (Q) for a partition in communities $m = [m1, ..., mn]$ of a weighted undirected graph is defined (Rubinov & Sporns, 2010; Newman, 2006; Watts, 2004) as:

$$Q^{w}_{(m1,\ldots,mn)} = \frac{1}{l^{w}} \sum_{i,j \in N} \left[w_{ij} - \frac{k_i^{w} k k_j^{w}}{l^{w}} \right] \delta_{mi,mj} \quad \text{(Eq.4)}$$

where w_{ij} is the weight of the edge between node i and node j. The set of weights fits into a matrix w that represents the graph G. Here w_{ij} is the correlation between the row i and row j of functional O_2Hb matrix. Rows and columns of the square matrix G are indexed by the nodes of G (that is the time index of O_2Hb matrix). When connections are non-oriented (as in the present study) this matrix G is symmetric: weight $w_{ij} = w_{ji}$ and k_i is the weight of vertex i that is the sum of w_{ij} for all vertices j. The number l^{w} is the total sum of weights. Modularity optimization was done based on the assumption that a graph partitioning is the difference between the number of edges within the partitions found and the number of expected edges at random between vertices of an equivalent degree distribution (Newman, 2006). In this formalism, the ratio $k_i^{w} k_j^{w} / l^{w}$ gives the null model, that is the probability that a random edge with a random weight w_{ij} joins the nodes i and j (Newman, 2006). Nodes of G are partitioned between the sets $m1,\ldots,mn$. So, m_i is the set of the actual partition that contains vertex i. The $\delta_{(mi, mj)}$ (delta of Dirac) function for given vertices i and j takes the value 1 if i and j are in the same subset of the partition (that is $m_i = m_j$), and 0 otherwise. Importantly, in our study we used the modularity analysis across all time steps and not for each graph. We then considered that distinct community detected should reflect different network organization without extract the exact topological organization. We determined the communities in each of these graphs by the algorithm that maximizes the modularity (see Eq.4) from the Brain Connectivity Toolbox (Rubinov & Sporns, 2010).

2.5.3. Statistical analysis

After normality testing (Lilliefors test), between-group differences were tested using one-way ANOVA on the three tapping performance variables (mean, CV and drift of ITI series), and on MF-Width with respect to our main hypothesis. Secondarily we also checked for any between-group difference in the mono-fractal exponent (α). We used Kruskal Wallis analysis, as the data were not normally distributed for the three sliding window sizes of community detection analysis. We used Spearman's correlation between the number of networks detected for each sliding window size (30 s, 75 s and 120 s) and MF-Width of the tapping series.

3. Results

3.1. Tapping performance

All samples of the tapping performance variables (mean, CV and drift) were normally distributed. Our experimental design was thought to impose different levels of constraints to the subjects without inducing differences in tapping performance. The ANOVA applied to the performance showed no significant difference between groups for all variables (mean: $F(3, 28) = 1.519$; $p = 0.230$; $\eta^2 = 0.136$, CV: $F(3, 28) = 2.316$; $p = 0.523$; $\eta^2 = 0.045$, drift: $F(3, 28) = 0.634$; $p = 0.594$; $\eta^2 = 0.022$, Figure 3D).

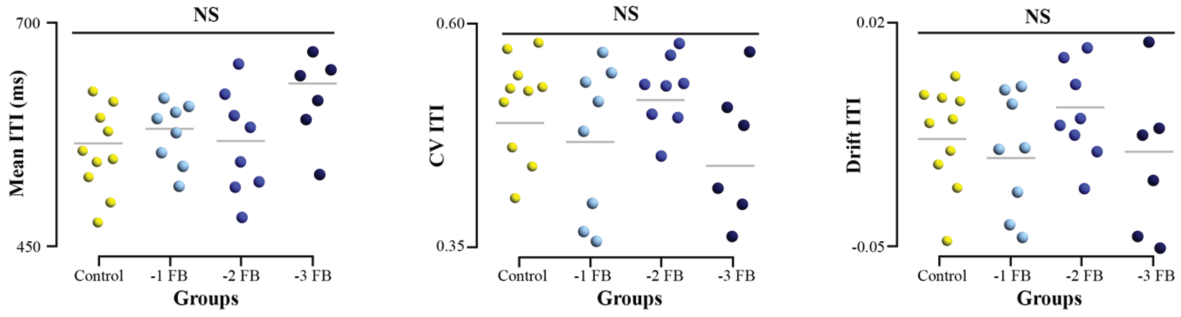


Figure 3D: Dotplot of tapping performance for the four groups. Left, mean inter-tap intervals (ITI) produced. Middle, Coefficient of variation (CV) of ITI series. Right, drift of ITI series during the task. Error bars represent standard error.

3.2. Multi-Fractal Properties of Tapping Series

MF-Width samples were normally distributed after log-normal correction. The one-way ANOVA revealed a significant group effect ($F(3,28) = 2.822$; $p = 0.044$; $\eta^2 = 0.253$). LSD Fisher *post- hoc* showed differences between the control group and the −1 FB and −2 FB groups ($p = 0.012$ and $p = 0.021$, respectively). Figure 3E summarizes the results obtained for the multi-fractal properties of tapping time series. Mono-fractal exponents (α) were normally distributed, and the one-way ANOVA did not show any significant difference between groups ($F(3,28) = 0.845$; $p = 0.473$; $\eta^2 = 0.071$).

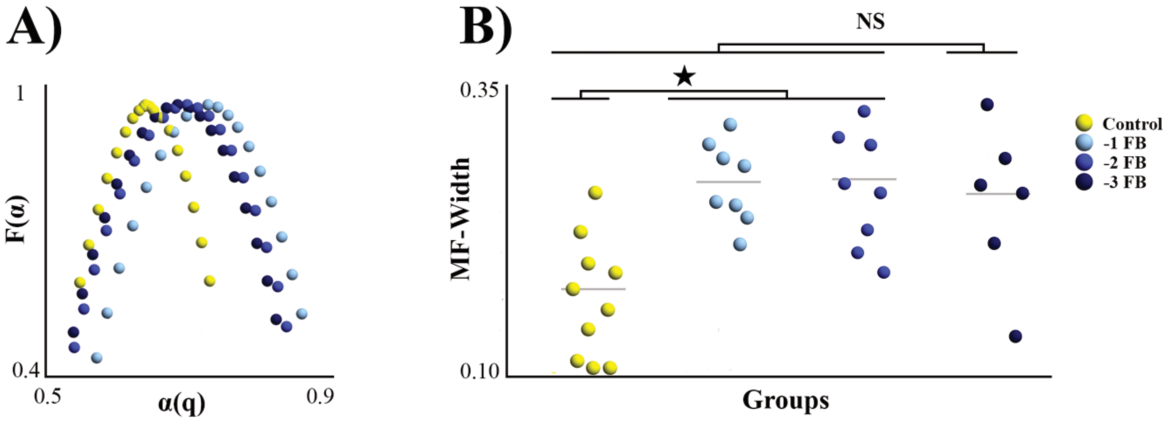


Figure 3E: Degree of multi-fractality of ITI series (MF-Width) for the four experimental groups. **(A)** Average multi-fractal spectrum for each group. **(B)** Dotplot MF-Width for the four experimental groups; gray horizontal line represent the mean. Star reflects the significant difference at $p < 0.05$.

3.3. Modularity Analysis

For all considered sliding window sizes, Kruskal Wallis test showed significant differences between Control and −1 FB, −2 FB and −3FB groups (for 30 s: $H(3) = 18.7$, $p = 0.003$; $\eta^2 = 0.561$; for 75 s: $H_{(3)} = 18.5$, $p = 0.001$; $\eta^2 = 0.554$; for 120 s: $H(3) = 18.9$; $p = 0.003$; $\eta^2 = 0.568$). All corrected *p*-values for multiple comparisons are reported in Table 1. Results for each window size are shown in Figure 3F.

TABLE 1 | Corrected *p*-values of Kruskal Wallis analysis for each sliding window size. (*Significant differences are in bold.)*

	Window size		
	30 s	75 s	120 s
Control / -1 FB	**< 0.009**	**< 0.04**	**< 0.03**
Control / -2 FB	**< 0.003**	**< 0.0002**	**< 0.02**
Control / -3 FB	**< 0.006**	**< 0.02**	**< 0.01**
-1 FB / -2 FB	1	1	1
-1 FB / -3 FB	1	1	1
-2 FB / -3 FB	1	1	1

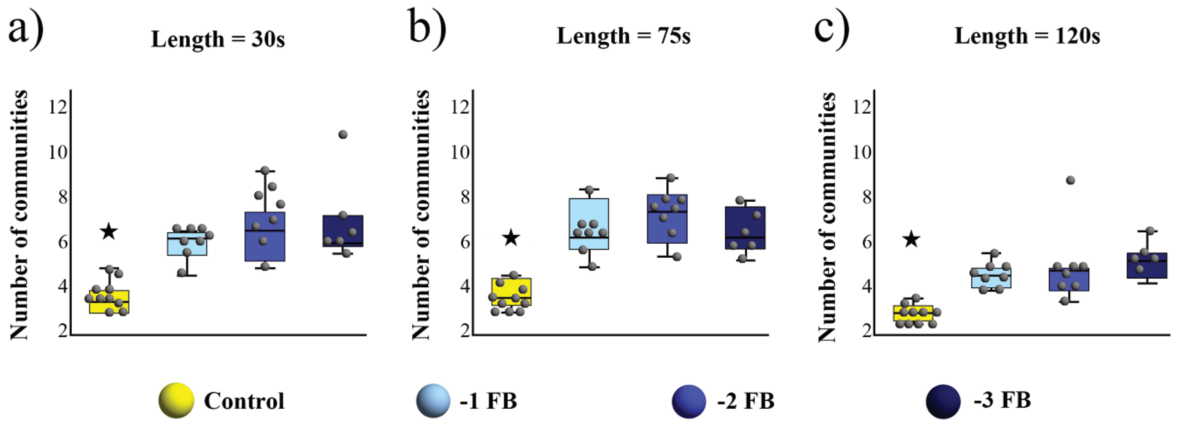


Figure 3F: Box plots with median, quartiles, and individual dots for the number of communities detected during the task for the four groups (Control, −1FB, −2 FB, and −3 FB), for **(A)** sliding window of 30 s, **(B)** sliding window of 75 s, and **(C)** sliding window of 120 s. Stars highlight significant difference at $p < 0.05$.

3.4. Relationship Between Modularity in the Brain and Fractal Properties in Behavior

With regard to our main hypothesis, results showed a significant correlation (Figure 3G) between MF-Width in tapping series and the number of brain networks detected for window sizes 30s (rho = 0.277; p = 0.028) and 75 s (rho = 0.275; p = 0.038). However no significant correlation was found for window size 120 s (rho = 0.086; p = 0.526).

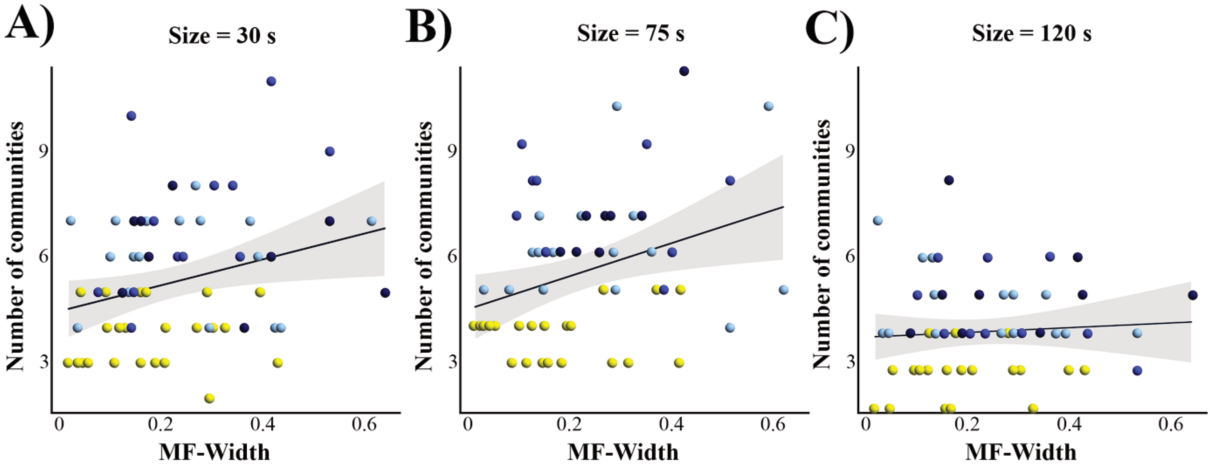


Figure 3G: Scatterplots showing the correlation (Spearman's correlation) between the multi-fractal properties (MF-Width) and the number of communities detected with modularity analysis, for **(A)** window size = 30 s, **(B)** window size = 75 s, and **(C)** window size = 120 s. The correlation is significant for 30 and 75 s windows. Yellow = control group, light blue = −1 FB, blue = −2 FB, and dark blue = −3 FB group.

4. Discussion

The present study aimed to establish a relationship between connectivity patterns underlying adaptation at the brain level and fractal properties as their dynamic signature in the behavior. We hypothesized that the number of brain networks involved in the task and the multifractal properties of the tapping series would evolve jointly, as a function of different conditions of feedback deprivation. We found that (i) the degree of multifractality (MF- Width) increased significantly in groups where feedbacks were suppressed as compared to the control group; (ii) the number of networks involved during the task was higher for groups with feedback deprivation than for the control group; and (iii) MF- Width and the number of networks involved in the task were correlated for sliding windows of 30 and 75 s. After discussing the suitability of the experimental design, we consider some notable implications of our results at the behavioral and brain levels, respectively, before focusing more specifically on the brain-behavior relationship.

4.1. Suitability of the Experimental Design

We considered the general definition of adaptability as the capacity to maintain a given function or performance despite changing constraints (De Wolf and Holvoet, 2005), also referred to as robustness (Whitacre, 2010). In this line,

the experimental paradigm was required in order to impose different experimental constraints while leaving the global level of task performance substantially close: the system was thus deemed to handle adaptations—notably reorganization in brain—allowing for sustained performance. To meet these requirements, we used a finger-tapping task. A major advantage of such task was to allow for a simple manipulation of the amount of sensory feedbacks available (–1 FB, −2 FB, −3 FB), while overall tapping performance has previously been shown insensitive to feedback manipulations (Aschersleben and Prinz, 1995, 1997; Repp and Su, 2013). That is, in the present study feedback manipulation has merely constituted a means to constrain the system and induce putative internal adaptation/reorganization, without any specific hypothesis as regards the sensory modalities. In this respect, our results are congruent with the literature (Aschersleben and Prinz, 1997), as we observed no significant differences between conditions of feedback deprivation in any of the three variables commonly characterizing tapping performance (mean ITI, CV and drift; Figure 3D). Moreover, such tapping task has previously been shown to entail fractal properties in the ITI series produced (Lemoine et al., 2006; Torre & Delignières, 2008). Our present results on the mono-fractal exponent α are also in agreement with the literature in this respect ($\alpha = 0.75 \pm 0.13$ all groups taken together, without significant differences between groups).

As regards the experimental design, we opted for an independent group design rather than repeated measures. Although this methodological choice obviously entailed limitations of sample sizes for each group, we deemed it preferable given the lengthy duration of tapping trials required for reliable fractal analysis (Delignieres et al., 2006; Vaz et al., 2017). Indeed, we aimed to observe the effect of adaptations due to feedback deprivation, which implied avoiding as much as possible any putative effects of weariness and attentional fluctuations that may also alter the fractal properties of tapping series (Damouras et al., 2010). Finally, in contrast to previous studies we here investigated a motor task with adaptations being experimentally induced by different levels of task constraints. In return, this approach implied some *a priori* uncertainty as regards the precise effect of experimental constraints especially on brain connectivity, rather than *a priori* controlled variations as possible in simulation studies for example. All in all, the consistency of our results with previous literature leads us to consider the

experimental design suitable, and following results with reasonable confidence.

4.2 Multi-fractal Properties Reflect Adaptations Underlying Unchanged Performance

Further gain of precision in appraising the functional significance of fractal properties in behavioral variables is a still-open challenge. A significant body of literature has converged to the general idea that mono- and multi-fractal properties are a hallmark of the adaptability of biological systems (Goldberger et al., 2002; Lipsitz, 2002). However, such conclusions mostly originate from indirect cross- sectional observations revealing loss of fractal properties with aging, pathology, or different conditions of functional impairment that are generally associated with loss of adaptability (Manor et al., 2010; Manor and Lipsitz, 2013). Though adaptability (or loss of adaptability) may indeed constitute a common denominator, several potentially confounding effects, including effective adaptations to achieve task performance despite functional impairment, might actually be the cause of altered fractal properties (Dingwell and Cusumano, 2010).

Our present results show significant variations of multi-fractal properties as a function of feedback deprivation imposed to the system (Figure 3E) without significant functional decrement (Figure 3D), which does not appear directly relevant to the issue of adaptability. At a first glance, this result may appear congruent with previous studies showing an alteration of mono-fractal properties as a function of the involvement of sensorial feedbacks in task performance (Slifkin and Eder, 2012, 2014): it has indeed been proposed that weaker mono-fractal properties may be due to tighter sensorimotor control mechanism exerted on task- relevant variables (Dingwell and Cusumano, 2010; Warlop et al., 2013). However, we observed that the degree of multi-fractality in tapping series increased in feedback deprivation conditions compared to the control group. Mono- and multi-fractal properties do not capture the same features of time series: whereas mono-fractal properties summarize a homogeneous scaling behavior over the whole time series, multi-fractal analyses assess the possibly inhomogeneous scaling regimes present in the series, and capture the amount of intermittent changes in the systems/subjects functioning modes (Ihlen and Vereijken, 2010). Thus, this result suggests an increasing involvement of different modes of regulation to achieve unchanged performance despite the imposed experimental constraints.

Accordingly, we support the idea that rather than globally reflecting the adaptability of complex biological systems, changes in multi-fractal properties reflect effective adaptations underlying invariance of functional outcome.

In this line, characterizing multi-fractal properties in macroscale variables may constitute a fine-grained analysis to uncover masked adaptations underlying goal achievement. From a broader perspective, disentangling adaptability and effective adaptation actually constitutes a major challenge, as both come necessarily together to a certain extent (Ulanowicz, 2002). Combining analysis at the task-relevant observation level (e.g., the level of motor performance) and an assessment of the correlates occurring at underlying observation levels (e.g., the level of brain dynamics) may contribute to this end.

4.3. Changes in Brain Modularity Reflect Functional Adaptation to Constraints

In this study, we hypothesized that the variety and intermittency of functional connectivity patterns would be influenced by different conditions of privation of sensorial feedbacks. Our results show that dynamical reorganizations of the brain network yielded multiple networks that were intermittently involved during task performance (Figure 3F), and that the number of different networks involved depends on the experimental group, i.e., on the feedbacks subjects were deprived or not. The literature studying brain networks involved in a task has generally considered that for a given function or performance the functional organization of the brain is stable over time. Accordingly, the purpose of investigations has often been to extract the typical network engaged in a given task, using a number of computational methods (Biswal et al., 1995; Witt et al., 2008). Nevertheless, another part of the literature studying the dynamic properties of functional networks in resting state has showed that the modular organization of the brain evolves within the scanning period (Chang & Glover, 2010; Hutchison et al., 2013; Fallani et al., 2014) and that such natural fluctuations are likely to support the ability of quick adaptive responses (Deco et al., 2011). Previous studies using resting paradigm do not enable to reveal the actual implementation of such adaptability during a sensorimotor task. These results complement previous literature insofar as they show that the variety of brain networks that are involved in a single task depends on the experimental constraints imposed to the subjects. More precisely, the counter-intuitive character of these results (i.e., increased number of networks with decreasing feedbacks, Figure 3F) could be

explained by the fact that, under constraints, the brain navigates between numerous networks to find out the solution enabling achievement of its level of performance (Kelso et al., 2013; Tognoli & Kelso, 2014). Such explanation seems consistent with previous studies showing novel recruitment of cortical areas under conditions of chronic sensorial deprivation (blindness, deafness, Merabet and Pascual-Leone, 2010), although adaptation to transient experimental manipulations is not directly comparable with lifelong alterations.

From a broader perspective, considering that the brain possesses degenerate properties (i.e., multiple networks could perform the same function with some of them being possibly latent, Edelman and Gally, 2001), the networks involved in a given function or performance can hardly be grasped in a comprehensive way without imposing internal and/or external constraints so as to induce variation in connectivity patterns (Price and Friston, 2002). This idea was initially developed in theoretical papers, and few experimental tasks actually allow imposing constraints without changing the motor performance. Electroencephalography, functional magnetic resonance imagery and fNIRS studies (Nedelko et al., 2010; Leff et al., 2011; Muthuraman et al., 2012) showed that the sensorimotor network (e.g., M1, PMC, and PFC) is engaged in a simple short finger- tapping task and is supposed to reflect sensory integration, motor initiation and production. Conversely, our results suggest the existence of multiple networks that allow for the carrying out of a tapping task over time. Moreover, there is no single network dedicated specifically to tapping independently of the different conditions under which tapping is to be performed. However, these findings need to be examined with caution due to some methodological consideration. In this study, we used modularity analysis (or community detection, Newman, 2006; Sporns, 2012 ; Sporns and Betzel, 2016) at the macro scale level (between networks) and not on each network. One can hypothesize that the latter analysis would make it possible to highlight similar clusters of sub-networks linked in different ways. In particular, it has recently been shown that dynamic connectivity between different brain regions is not only dependent on the regions involved, but also on the interconnections between multiple EEG frequency bands (Liu et al., 2015). Future investigations using EEG combined with fNIRS would allow to better understand the dynamic functional organization of the brain, and the role of multi-frequency connections in network coupling**.** It has been proposed that the

modular organization of the brain is subtended by a relatively rigid network composed of nodes distributed in each sub-module (Sporns, 2013). Nevertheless, although the origin of temporal fluctuations in dFC estimates remains largely unknown, sliding window analysis was shown as a promising method to highlight dynamic connectivity in multiple neuroimaging methods. As the optimal window size to compute correlation coefficient is still under debate (Hutchison et al., 2013), we used three-window sizes (30, 75, and 120s, see Figure 3F) to be confident in the results obtained. We found a strong statistical difference between the control group and other groups independently of the window size. This confirms our hypothesis and this allows us to confirm that our results are not dependent on the window size chosen (e.g., Hutchison et al., 2013; Hindriks et al., 2016). An additional step of our promising results would be to extract the characteristics of the different networks implemented with more fine-grained tools like those proposed in fMRI (Bassett and Bullmore, 2006; Bassett and Gazzaniga, 2011; Papo et al., 2014).

4.4. Bridging the Gap Between Brain and Behavior

The literature has mostly been studying the dynamics of cerebral networks on one hand, and the temporal structure of behavioral variability on the other hand, though both communities share key concepts coming with the complex system approach (Bullmore et al., 2009; Werner, 2010; Whitacre and Bender, 2010; Sleimen- Malkoun et al., 2014). Thus, attempts to link these two approaches seem valuable (Price and Friston, 2002; Friston and Price, 2011). In the present study, we provide novel evidence that the number of networks involved during a motor task in four experimental conditions significantly correlates with the degree of multi-fractality found in the sensorimotor outcome. This correlation was obtained for two of the three window sizes used (30 and 75s). Previous literature has highlighted that the dynamics of functional connectivity increase with diminution of the window size, due to the non stationarity of Blood Oxygenation Level Dependent or fNIRS signals for short windows with an increase of transient nodes that were unobserved for large window size (Hutchison et al., 2013). Therefore it is not surprising that fewer networks were detected for our largest window (120 s). As a consequence the correlation between the number of networks and the multi-fractal properties of tapping series was low and not significant for the 120 s window as compared to the smaller windows.

Previous theoretical and simulation approaches had shown that degeneracy plays a central role in the link between complexity, adaptability, and robustness (Whitacre, 2010) and that degeneracy may underlie fractal properties in the outcome variables (Delignières and Marmelat, 2013). Our result provides experimental support highlighting the link between theoretically related properties across two different scales of observation, namely between degeneracy at the level of brain connectivity and measures of complexity at the level of behavior, both being considered tightly related with systems adaptability. As such this result may be of particular relevance for translational research, since a significant part of literature has proposed to assess the diagnostic and/or prognostic power of fractal properties in sensorimotor variables in neurodegenerative pathologies (e.g., Parkinson or Alzheimer diseases) conveying the strong but so far experimentally unproven assumption that alterations of the brain network would come out in the fractal properties of behavior. Consequently, we consider that (i) fractal properties in macroscale variables are (at least partly) dependent on the degenerate organization properties of the brain, and (ii) concomitant changes in network connectivity and multi-fractal properties in behavioral variability reflect (at least partly) effective adaptations underlying invariance of functional outcome.

Finally, the system's ability to adapt and effective adaptation go hand in hand (Ulanowicz, 2002), the first being a necessary condition for the latter, the latter in turn affecting the first. To be able to disentangle the brain and behavioral correlates of adaptability and adaptation is of importance seeing that evolution toward pathological states or advancing age often come along with a decreased ability to adapt, up to functional loss (Lipsitz, 2002; Manor et al., 2010; Stergiou et al., 2016). The joint analysis of motor variability and brain dynamics, as well as the use of an experimental paradigm that allows to gradually constraining the system so as to induce adaptations (maintenance of performance) up to the loss of further capacity to adapt (decrement of performance), may contribute to this end. Extending the present tapping paradigm may be appropriate in this view since, in contrast to visual, auditory or tactile feedbacks, further deprivation of proprioception has been shown to decrease tapping performance (Stenneken et al., 2006). Our present experimental design was not conceived such as to allow for investigation of putative differential effects among sensory modalities (e.g., auditory

and visual cortex), and we limited ourselves to the assessment of sensorimotor and prefrontal regions. Future studies using a larger number of channels (whole brain) may examine in how far the networks dynamics underlying finger tapping are affected depending on the sensory modality suppressed.

4.5 Conclusion

To what extent the multiple networks in the brain restructure with some distinctive properties of motor variability has remained unanswered so far. Both conceptual considerations and simulation approaches have provided strong indications for such relationship but experimental evidence has been lacking. Our present work evidences a significant correlation between the number of brain networks and the degree of multi-fractality in tapping. We believe that this finding constitutes a step further toward bridging the gap between the degenerate connectivity patterns at the brain level and the properties of variability at the behavioral level. We anticipate that future work, possibly combining simulation and experimental methods like multimodal neuroimaging, will provide means for larger and/or more fine-grained ranges of variation in the number of brain networks involved and the fractal properties of motor performance, so as to further consolidate our present findings.

Author contributions

All authors contributed to this study. GV, KT, and SP conceived and designed the study. KT, MM, and SP provided funding. GV performed the experiments. GV, MM, and SJ analyzed the data. GV, KT, and SP wrote the paper and SJ and MM edited the manuscript.

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2nd Transition

From undirected to directed brain networks connectivity

The second study of the dissertation indicated a possible link between multi-fractal properties at the macroscopic scale of observation (behavioral response) and intermittency of dynamic functional connectivity in the brain (the number of brain networks involved, Figure 3G). Nevertheless, some methodological limitations should be noticed and could be taken into account in the future. As the fNIRS used was not composed of short channels regressors or external physiological triggers, our fNIRS signals were possibly influenced by confounding factor such as the scalp blood flow increase without evoked cerebral activation. Although we are aware of this possible limit, we currently have no opportunity with the tools in our possession to address this factor but we can nevertheless think that this phenomenon would remain constant in the accomplishment of our task in particular because it's not expensive physiologically. Nevertheless, our study constitutes the first stone for future investigations linking both the dynamics of the networks used in carrying out a motor task and the variables extracted at the behavioral level. It opens up the possibility to better distinguish effective adaptation in the achievement of a task from the adaptability potential.

Our positioning in this work concerning the distinction between the potential of adaptability and adaptation (effective or not) leads us to consider in a complementary way in future studies the system's evolution capacities (Figure 3H) in conjunction with its robustness as studied in the two studies presented above (see chapter 2 and chapter 3). This distinction will therefore be essential especially in the quest for the discovery of sensorimotor markers of health. Moreover, from a more systematic point of view, the use of the fNIRS alone does not allow to investigate different levels (particularly cerebral) to test the biological hypothesis of a dynamic cascade organism or self-organized criticality. Finally the key concept at the heart of the hypothesis of our previous study (Degeneracy, Chapter 3) questions in view of our results. In fact, in their two original studies, Delignières & Marmelat (2011, 2013) proposed that a minimal number of networks "are necessary" to produce long-range correlated series. Although our results concerning the functional dynamics investigated by fNIRS put forward for each of our experimental groups several networks, we can ask the question of the possible "minimum number". If this value (or variable) seems relevant, the tool and the method to quantify it faithfully remain suspended.

While we are among the first team to our knowledge to compute dynamic functional connectivity with fNIRS during a continuous motor task, it seems critical to develop more advanced approaches to minimize certain limits when using the Pearson correlation. As

highlighted in some studies (Hutchinson et al., 2013; Hidrinks et al., 2016), there are possible methodological improvements concerning the functional connectivity analysis used (Bivariate Pearson correlation analysis). A first limitation is the choice of the window length we set a priori to compute the correlation coefficient. While we used three window lengths (30 s; 75 s; 120 s), there is currently no consensus on the optimal window especially for an application on biological signals that are reflected to be nonlinear. The second limitation is the possible multiple interactions between the large number of time series obtained in a single recording at multiple possible overlapping brain space. Like mass univariate analysis, bivariate Pearson's correlation could be subject to the transitivity effect (the link between signal x and signal y could be mediated indirectly by a third signal z). Multivariate analysis seems therefore a potential promising approach to limit the possible effect of transitivity in connectivity analysis. Finally, maybe more important from a fundamental point of view, Pearson's correlation is not able to reflect the directionality of the link between time series. A high level of correlation could be sustained by a bi-directional link between two regions of interest or a high dependency of one region to another. Taking into account the information flow propagation is a step forward simple description of a non-directed network and was the purpose of multiple research teams since twenty years. Although methods commonly used in fMRI such as dynamic causal modeling is an interesting approach, this one is based on structural connections prerequisites to create and validate the implemented model. Another approach, based on an autoregressive model quantifies the directionality of the link between two (or more) time series without being dependent on knowledge of the underlying system (model free). This approach initially proposed by Granger (1969) is the subject of a box (box 3) and will be the initial starting point of some methods proposed in the following study. Given the above limitations of our previous approach, we decided to apply a recently published method to highlight better the dynamic directional connectivity between brain signals from fNIRS measurements during the finger-tapping task.

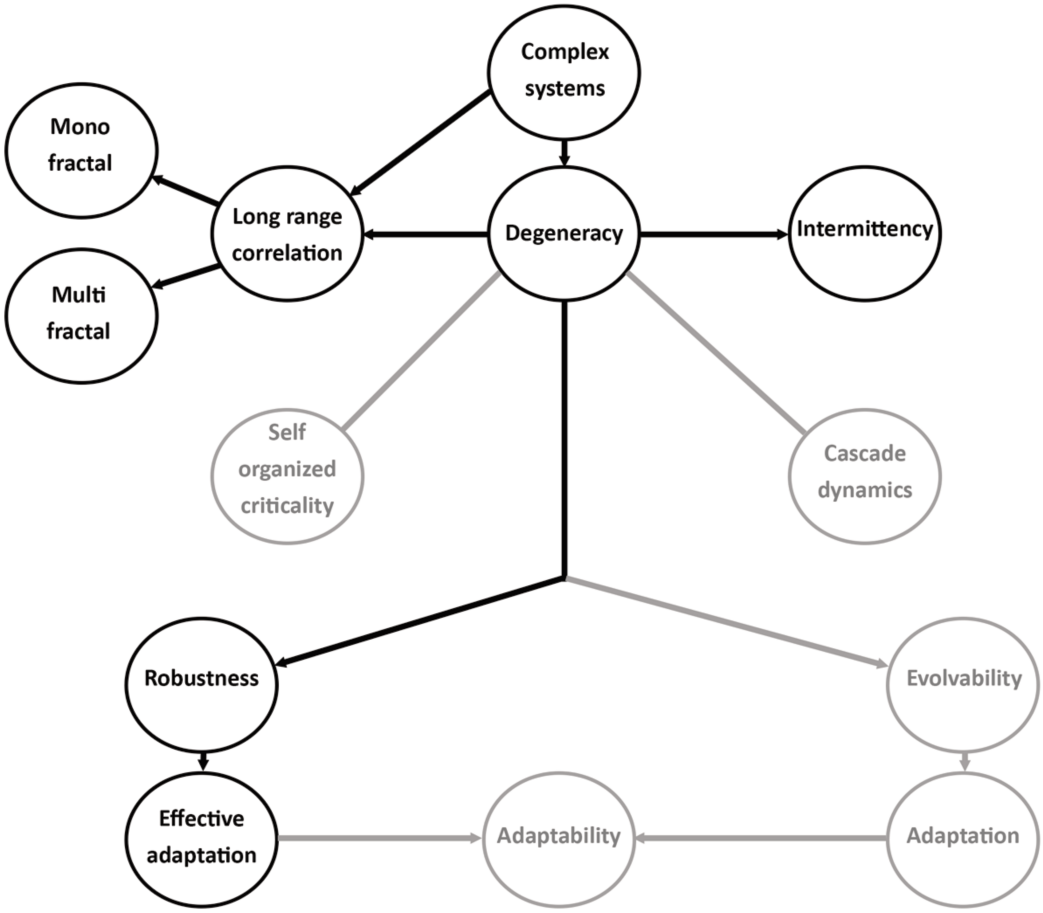

Figure 3H: Diagram representing the key words studied in the study 2 of the dissertation. This 2nd study investigated the concept of degeneracy and its intermittent properties.

Box 3

Granger Causality

"In this paper, we analyze fundamental properties of Granger causality and illustrate statistical and conceptual problems that make Granger causality difficult to apply and interpret in neuroscience studies"

(Stokes & Purdon, 2017)

"However, these claims rest, respectively, on an incomplete evaluation of the literature, and a misconception about what GGC can be said to measure"

(Barnett et al., A response to Stokes and Purdon, 2017)

When are two "structures" connected? It is by this essential question that we introduce this box. We know today from numerous studies published since the late 90's that cerebral functioning is organized within a network (Friston et al., 1993, 1995, 1997; Biswal et al., 1995). Many studies (including those presented in Chapter 3) have relied on correlation analyzes not only because it is one of the oldest methods applied in fMRI (Biswal et al., 1995) but also because it is relatively simple to understand and study in most undergraduate courses. Nevertheless, this method has already been shown for a long time to be limited and inadequate in most cases (Baccalá & Sameshima, 2001). One of the first drawbacks encountered is the transitivity problem indicated previously. Although two signals can be strongly correlated, this bivariate analysis does not make it possible to reflect if this

correlation is driven by a third element unmeasured or not take into account due to the mathematical analysis. Moreover, this approach does not make it possible to highlight directionality in the link uniting two structures. Are they interrelated or does one "structure" direct the other? A visual comparison between networks extracted from correlation analysis and multivariate granger causality analysis is presented in figure 3I for one representative subject during two conditions (resting state and motor task).

It is one main reason that led Granger (1969) to develop a mathematical analysis to assess directionality based on a conceptual idea proposed a little earlier by Wiener (1956). The relatively simple idea underlying this mathematical formalism is that (i) a cause occurs before it's effect and (ii) some form of causality between a time series *x(n)* to another series *y(n)* may be at play if knowledge of *x(n)*'s past observation is helpful in predicting the actual value of *y(n)*. In fact, with this approach, we can only say that the past observations of *x(n)*'s help to predict the value of *y(n)*. This is the basis of this mathematical approach. The term "causality" in the sense of Granger could then be seen as a confounding with the common sense of causality. Studies therefore proposed to use the term "G-causality" or "Granger-Geweke Causality" (Sameshima & Baccalá, 2014; Barnett & Seth, 2014; Barnett & al., 2017).

G-Causality is a popular and powerful analysis method in neuroscience (Seth et al., 2015) although there are debates in the literature (see for instance an article by Stokes & Purdon in 2017) especially in the interpretation of the results obtained with this method. These last authors (Stokes & Purdon, 2017) first highlight the fact that Granger Causality and how it is commonly used can be severely biased by some preprocessing steps or of high variance (inter and intra subject variability). Second, G-Causality does not reflect the structural and true causal mechanisms of a system (Friston 2011). Nevertheless, following the publication of this article, many voices rose and criticized this article in a relatively virulent way (see for exemple Barnett et al., 2017; Faes et al., 2017). This last reference in particular is very aggressive as evidenced by these two quotes:

"We think that Stokes and Purdon use a formulation of G-Causality which is outdated"

"It would be a pity if this paper, even if written in good faith, became a wildcard against all possible applications of GC, regardless of the large body of work recently published which aims to address faults in methodology and interpretation."

To conclude, analyzes such as those initially proposed by Granger suffer from certain limitations in the same way as any analysis used whatever the field of investigation. Nevertheless, many mathematical developments make it possible to limit the problems posed by these approaches, in part for example with the toolbox proposed by Barnett & Seth (2014) or dynamic "Causality" (Anwar et al., 2013; Zanin & Papo, 2017).

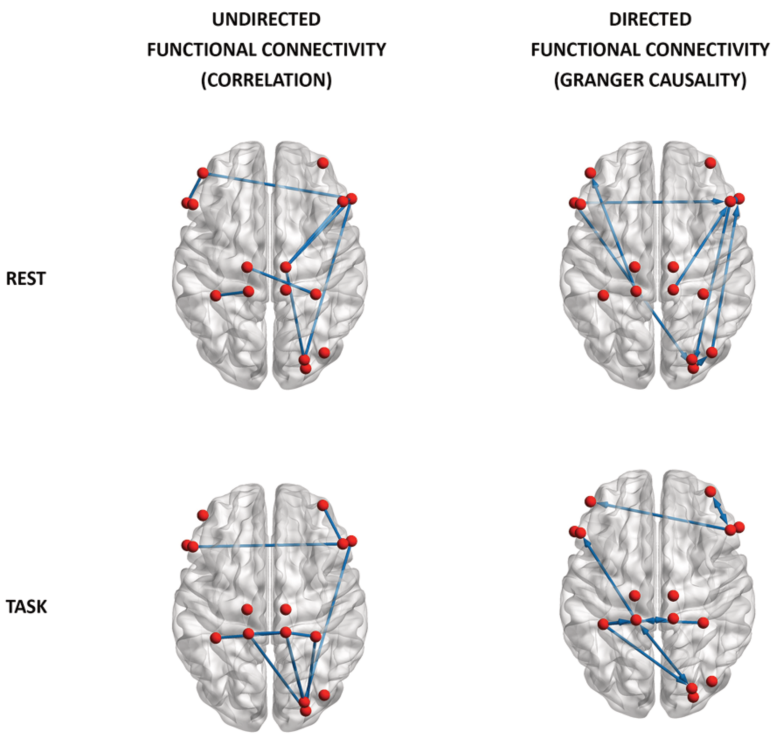

Figure 3I: Comparison between undirected functional connectivity (FC) and directed FC performing resting state condition (upper panel) and ergocycle task (lower panel) for one representative subject. Data represented for each condition/method was threshold at the 5% of the strongest edges. Edges are bi-directional (non directed) on the left part of the figure (Correlation) and bi-directional or unidirectional (directed) on the right part (Multivariate Granger Causality analysis). Data as part of a Master study (L. Borrot, 2018).

Chapter 4

Dynamics of the human brain network revealed by time-frequency effective connectivity in fNIRS

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Abstract:

Functional near infrared spectroscopy (fNIRS) is a promising neuroimaging method for investigating networks of cortical regions over time. We propose a directed effective connectivity method (TPDC) allowing the capture of both time and frequency evolution of the brain's networks using fNIRS data acquired from healthy subjects performing a continuous finger-tapping task. Using this method we show the directed connectivity patterns among cortical motor regions involved in the task and their significant variations in the strength of information flow exchanges. Intra and inter-hemispheric connections during the motor task with their temporal evolution are also provided. Characterisation of the fluctuations in brain connectivity opens up a new way to assess the organisation of the brain to adapt to changing task constraints, or under pathological conditions.

1. Introduction

Functional near-infrared spectroscopy (fNIRS) is a non-invasive imaging technique that has become increasingly popular for brain function research in recent years (Ferrari & Quaresima, 2012; Scholkmann et al., 2014). Based on the exploration of hemodynamic signals, in the same way as functional magnetic resonance imaging (fMRI), and its blood oxygen level dependent signal, fNIRS provides information on the functionally evoked changes in cortical oxyhemoglobin (HbO) and deoxyhemoglobin (HHb) concentrations with relatively low spatial resolution. However, due to several technical advantages (high temporal sampling rate, portability and ability to perform long data acquisitions), fNIRS has been extensively used to measure the magnitude of brain activation during motor or cognitive tasks, in both healthy and diseased populations (Gervain et al., 2008; Derosière et al., 2014; Sato et al., 2013).

Nevertheless, as highlighted by some authors, the brain is a complex system *par excellence* characterised by the co-existence of functional segregated parts of the brain, and functional integration among these parts (Sporns, 2012; Tononi et al., 1994). Functional specialisation, or segregation, implies that elements of the brain network tend to organise into separate, statistically independent areas. It refers to the idea that parts of the brain may, for example, specifically cope with the cognitive (Stoodley & Stein, 2013), perceptual (Price, 2012) or motor (Sun et al., 2007; Rao et al., 1996) components of a certain task. Functional integration, on the other hand, refers to the way these different components are connected to become statistically interdependent to some degree (Sporns, 2013). For example, an fNIRS study (Bajaj et al., 2014) in healthy subjects showed different changes in the link between motor cortex (M1), premotor cortex (PMC) and supplementary motor area (SMA) between various finger movement task conditions. By using fMRI, Grefkes and Fink (2011) showed relevant changes in intra- and inter-hemispheric brain links within the motor network after stroke. Therefore, a key challenge in neuroscience, in particular for portable and promising neuroimaging techniques such as fNIRS, is to move beyond identification of regional cortical activations toward the characterisation of interactions between brain areas (Seth et al., 2015).

Connectivity analyses of the brain have been the object of a growing interest in neuroimaging studies in recent years, and applied to both electrophysiology-based (electroencephalography (Lehmann et al., 2012); magnetoencephalography (Stam et

al., 2007; Muthuraman et al., 2014)) and hemodynamics-based (fMRI (Van Den Heuvel & Pol, 2010; Anwar et al., 2016); fNIRS (Mesquita et al., 2010; Anwar et al., 2013)) modalities. In this line, authors have often used bivariate Pearson correlation analysis in the time domain, or its counterpart, namely coherence in the frequency domain. While these analyses have shown their ability to distinguish between healthy and diseased populations (Van Meer et al., 2010; Park et al., 2011), they present limitations in two notable respects: first, they do not take into account the directionality of the link between two regions of interest. Furthermore, the time-series analysis of brain activity is typically limited to only two signals (bivariate analysis). That is, these types of analyses are known to not provide a comprehensive assessment of inter-channel interactions, as they ignore influences from other sources (Baccalá, & Sameshima, 2001).

In contrast to undirected functional connectivity, directed effective connectivity (EC) describes the influence that one region of the brain exerts on another. The two most commonly employed methods to analyse the directed influences within the whole brain network are Dynamic Causal Modelling (DCM) (Stephan & Friston, 2010) and Granger-Causality Modelling (GCM) (Seth et al., 2015; Granger, 1969). DCM is based on a statistical technique to highlight how well a model fits the data. In similar approach, structural equation modeling (SEM) (Zhu & Godavarty, 2013) comports a model where parameters are connection strengths or path coefficients between different variables. DCM and SEM were shown to product the same results (Penny et al., 2004). Because these two fixed models containing regions of interest need to be predefined, unknown brain areas or connections between areas cannot be investigated. While DCM and SEM are model driven methods based on assumptions between intrinsic and extrinsic linked areas, the advantage of GCM is that it does not require any *a priori* information, as it completely relies on the multivariate auto-regressive (MVAR) modelling of the recorded brain signals (Friston, 2009). Due to their assumption-free nature, GCM based methods are complementary to DCM (Friston et al., 2013). The first studies addressing directed connectivity have adapted Granger's formalism (Geweke, 1982; Seth, 2010), considering that some form of causality from a time series *x(n)* onto another time series *y(n)* may be at play, if knowledge of *x(n)'s* past behavior proves helpful in predicting *y(n)*. The two time-domain methods derived from Granger causality, the conditional Granger

causality (CGC) and partial Granger causality (PGC) (Guo et al., 2008), are particularly suitable for signals with very low signal to noise ratio. However, in biological time series, and notably in brain analysis, need is to deal with unmeasured latent variables and environmental (exogenous) inputs. For some signals, like local field potential signals, PGC has been proven more successful than CGC, notably in controlling for a third time series that could falsely cause connection between two series of interest (Roelstraete & Rosseel, 2012). However, CGC and PGC provide causality information only in the time domain (Hesse et al., 2003).

Aside from time domain causality methods, frequency-domain causality methods are able to look at causality at a particular frequency. Frequency-domain causality measures are also tolerant of wide ranges of noise. The directed transfer function (DTF) can quantify causality between different time series, but is unable to differentiate between direct and indirect connections (Kamiński et al., 2001) (where the connection *x* to *y* could be mediated by *z*). Therefore, two new developments of DTF methods were proposed, namely the directed DTF (Korzeniewska et al., 2003) and, recently, the non-normalized DTF, which overcomes the drawbacks of DTF and allows discrimination between the direct and indirect connections (Blinowska et al., 2016). Similar to DTF, partial directed coherence (PDC) is based on the Fourier transformation of the MVAR coefficient. Unlike DTF, PDC can differentiate between direct and indirect connections and is currently the most widely used method in biomedical signals. Its major shortcoming, however, is that any additional source affects the strength of already present sources, due to the fact that normalisation in the equation of PDC is done with respect to the sources (Sameshima & Baccalá, 1999). Yet, the generalised partial directed coherence can accommodate differences in the individual variances of the subjected time signals (Baccalá & Sameshima, 2007). The re-normalised partial directed coherence allows overcoming the limitation related to the addition of the source without requiring any frequency dependent significance level (Schelter et al., 2009).

Directional information provided by the aforementioned methods offers the potential for mapping directed influences between regions of the brain. However, different studies applying such analyses to fNIRS data (Holper et al., 2012; Zhang et al., 2014; Medvedev, 2014) have implicitly considered that patterns of connectivity were stationary within the scanning period: indeed, analysing the global (average) connectivity pattern over a relatively long time session conceals its temporal

evolution during the task. Though intermittence between functional integration and segregation in the brain leads to the idea that information flows between two brain areas are highly dynamic. Recent studies have shown that brain connectivity also evolves over time in a resting state, as it may do in continuous tasks (Chang & Glover, 2010; Hutchinson et al., 2013). Such dynamic brain organisation is actually a key property of any complex system that shows high adaptive capacities (Sporns, 2012), and time-frequency analyses can provide insight into it.

Here, we proposed to perform EC analyses based on a novel method applied in fNIRS, namely time-resolved partial directed coherence (TPDC) (Anwar et al., 2016; Anwar et al., 2013). TPDC has been developed and applied to EEG, MEG or fMRI signals (Anwar et al., 2016). This method is based on directed effective connectivity to compute a time-frequency analysis established on an MVAR model. Allowing the application over time of multiple PDC (Baccalá & Sameshima, 2001), TPDC makes it possible to account for the evolutions over time and frequency bands of the information transfer directed between multiple time series, i.e. between regions of interest, for probing diseased (Muthuraman et al., 2015; Choisa et al., 2017) or healthy brain (Muthuraman et al., 2014; Anwar et al., 2016).

To fully understand the functioning of the brain and its adaptive capacities, we have to take into account its dynamic organisation through the time-frequency evolution of connectivity patterns. The purpose of this study was therefore (i) to expose the TPDC method on fNIRS signals and (ii) to reveal the ability of the proposed method in assessing the time-dynamics of brain connectivity during a simple motor task performed by healthy subjects. To this end, we first present experimental fNIRS data collection. Second, we develop the TPDC computation steps. Third, we show results of this example application of the TPDC effective connectivity approach to experimental fNIRS data.

2. Materials and Methods

2.1 Participants

Six healthy volunteers took part in this study (aged 28.6 ± 3.8 years). All participants gave written informed consent before participating in the study. All participants were right handed according to the Edinburgh Handedness Inventory (Oldfield, 1971) and reported normal hearing and normal or corrected vision. None had any sign of neurological disease, nor reported extensive practice in music. All procedures were approved by the local

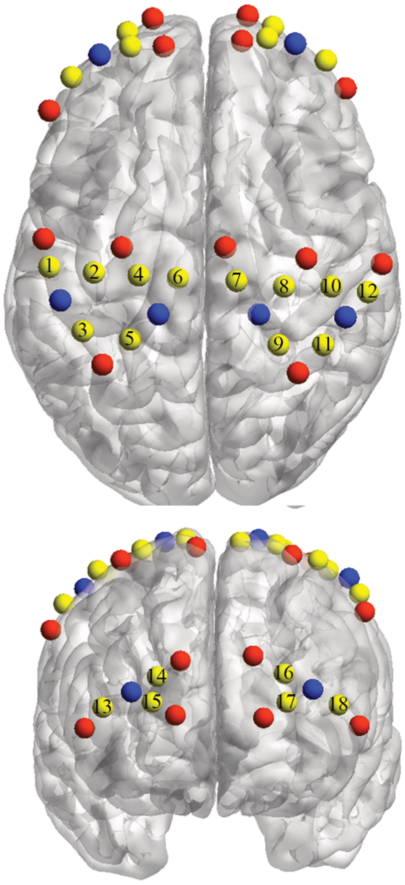
ethics committee and complied with the Declaration of Helsinki for human experimentation.

2.2 Experimental design

The experiment was conducted in a quiet and dimly-lit room. Participants were seated comfortably on an adjustable chair. They were instructed to remain relaxed and to refrain from extensive head motion. After positioning fNIRS probes over the head, fNIRS data recording was initiated, with a one-minute resting state (quiet baseline) while the subjects' eyes were open. It allows having the best possible baseline condition before the experimental task. Then, participants were asked to perform a continuous (6 minutes and 40 seconds) tapping task, according to a conventional synchronisation-continuation paradigm (Wing & Kristofferson, 1973). During the initial synchronisation phase (around 15 seconds), the tapping tempo was prescribed by a PC-driven auditory metronome delivering 20 signals at a frequency of 1.5 Hz. Once the metronome stopped, participants were requested to continue tapping by maintaining the prescribed tempo as accurately and regularly as possible for the whole trial duration. Data from the last 6 minutes of each trial was submitted for analysis.

2.3 Data collection

Changes in HbO and HHb were assessed using two continuous wave multi-channel near infrared spectroscopy systems (Oxymon MkIII and Octamon, Artinis Medical Systems, The Netherlands) at two wavelengths (Oxymon = 763 and 855nm, Octamon = 742 and 848nm). The sampling rate was set at 10 Hz. In the present study, we used 10 transmitters (pulsed laser) and 4 receivers (avalanche photodiode), which were coupled through fiber optic cables mounted onto a customised head cap. The 16-channel array with a transmitter-receiver spacing of 30 mm extended on three regions of interest: PMC, M1 and SMA in both hemispheres. In addition, the 2nd 8-channels system (Octamon, inter-probe distance of 35 mm) covered the dorsolateral (DLPFC) and orbitofrontal (OFC) cortices in both hemispheres. After positioning the head cap on the vertex location (Cz), a 3D-digitiser (Fastrack, Polhemus, United States) allowed the collection of the 24 probe positions (x,y,z space). In the present study, based on the selected 5 regions of interest (M1, PMC, SMA, OFC and DLPFC), 18 channels were retained for analysis. NFRI function (Singh et al., 2005) was used to extract the Montreal Neurological Institute coordinates (MNI). Localisation, MNI coordinates and Brodmann area (Chris rorden's MRIcro) correspondences are reported in Figure 4A.



Ch	MNI Coordinates			BA (%)
	x	*y*	*z*	
1	-54	-17	58	4 *(15)* – 6 *(85)*
2	-38	-19	71	4 *(01)* – 6 *(99)*
3	-42	-40	67	3 *(31)* – 4 *(64)* – 6 *(5)*
4	-22	-20	77	6 *(100)*
5	-25	-43	75	4 *(41)* – 6 *(59)*
6	-8	-22	78	6 *(100)*
7	13	-24	79	6 *(100)*
8	30	-24	75	6 *(100)*
9	28	-45	74	4 *(48)* – 6 *(52)*
10	47	-24	67	4 *(9)* – 6 *(91)*
11	44	-45	65	3 *(8)* – 4 *(72)* – 6 *(20)*
12	60	-26	54	3 *(1)* – 4 *(46)* – 6 *(53)*
13	45	57	14	10 *(21)* – 45 *(1)* – 46 *(78)*
14	24	65	26	9 *(6)* – 10 *(73)* -46 *(21)*
15	26	69	16	10 *(1)*
16	-25	62	27	9 *(4)* – 10 *(47)* – 46 *(49)*
17	-26	67	16	10 *(90)* – 46 *(10)*
18	-46	51	15	45 *(30)* – 46 *(70)*

Figure 4A: On the left, fNIRS probes location using BrainNet Viewer (Xia et al., 2013) with transmitters (in red), receivers (in blue) and channels (Ch, in yellow). On the right, mean MNI coordinates and Brodmann area (BA) correspondence for each channel.

2.4 fNIRS preprocessing

First, we extracted raw data (light intensity) from the ARTINIS software (Oxysoft v3.0.95). Data was then uploaded using a MATLAB (The MathWorks) in-house script, and converted to optical density (OD) (Huppert et al., 2009) defined by:

$$\Delta OD^{\lambda}_{ij(t)} = Ln\left[\frac{\Phi^{\lambda} ij(0)}{\Phi^{\lambda}_{ij}(t)}\right] (1)$$

where Φ is the intensity, i is a source position, j is a detector position, and λ the wavelength of light. Next, we applied the moving standard deviation and spline interpolation methods (Scholkmann et al., 2010) (SDThresh = 20, AMPThresh = 0.5, tMotion = 0.5s, tMask = 2s and p = 0.99), and then wavelet artefact correction (Molavi & Dumont, 2012) (with probability threshold α = 0.1) as recommended (Cooper et al., 2012), to remove possible motion artefacts. To access HbO and HHb relative concentration changes (Conc) (expressed in µM) we applied the modified Beer-

Lambert Law (Kocsis et al., 2006) to the OD data that included an age-dependent constant differential path length factor ($4.99+0.067*Age^{0.814}$) (Duncan et al., 1996).

White noise signal is one of the most harmful effects in connectivity analysis and can create spurious links, whether false positives or false negatives. As a consequence, we used a simple pre-processing step computing the power spectra to ensure the discrimination of noisy signals. For that purpose, we obtained the power spectra of each HbO time series (more sensitive to physiological noise than HHb) for each channel: detection of a peak value around 1Hz in the time series reflecting the presence of the heartbeat in the fNIRS signal (Themelis et al., 2007), was considered to indicate a good contact between the optode and the scalp. By running this pre-processing, 2 channels were removed in our 6 subjects, leaving 106 channels (18 channels per subject, minus 2 bad channels) to be used for the subsequent TPDC's analysis.

Subsequently, a linear detrending was used to remove slow drifts of Conc data, and time series were centered to zero mean to satisfy the criteria of second order stationary. Importantly, we did not use any filtering on our Conc data before further analysis, as it has been shown that filtering could lead to spurious connections (Barnett & Seth, 2011).

2.5 Time-resolved partial directed coherence

Using time-frequency causality allows for analysis of the temporal dynamics of the causality at any particular frequency in focus. The TPDC (Figure 4B) is based on dual-extended Kalman filtering (Wan & Nelson, 2001), and allows time-dependent auto regressive (AR) coefficients to be estimated. In general, the signals are analysed with static AR coefficients, meaning that the fitted model and the AR coefficients remain the same for the complete length of the signal. For non-linear signals like fNIRS, the model should be time varying and the coefficients need to be estimated regularly over the course of the time-period. Regularly estimating the coefficients is termed as adaptive auto-regressive process.

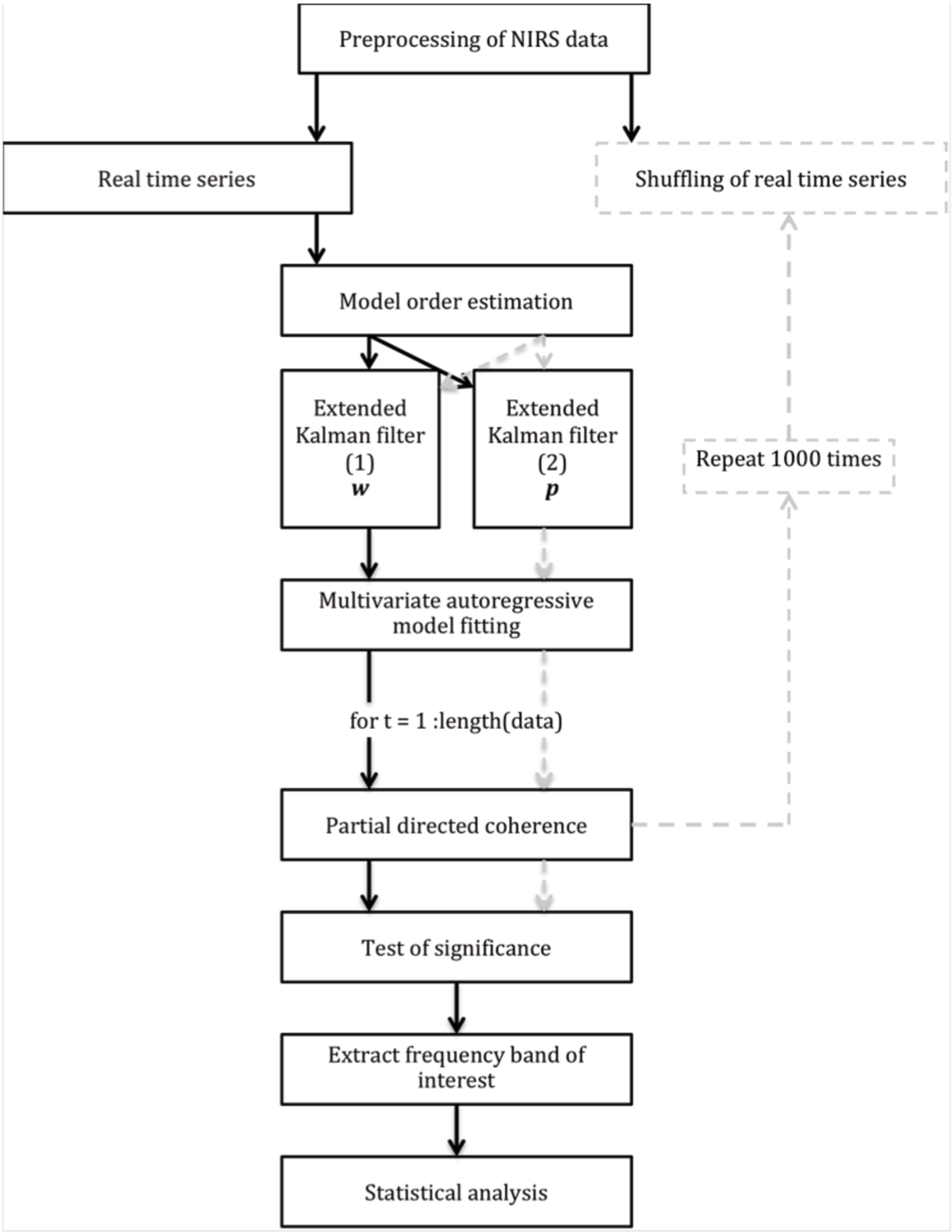


Figure 4B: Flow chart of the various steps used for the TPDC analysis. The black arrows and rectangles (left side) present the overall process using real fNIRS data. The dotted gray arrows and rectangles (right side) display the bootstrapping process undertaken.

The expression for an adaptive auto-regressive process can be given as follows:

$$x(t) = \sum_{r=1}^{r=p} a_r(t)x(t-r) + \eta(t)$$

where $a_r(t)$ are the time-varying MVAR coefficients, p is the model order of time series $x(t)$ and $\eta(t)$ is the zero-mean Gaussian noise process. To sum up, the extended Kalman filter used in the TPDC analysis is a predictor-corrector algorithm that estimates states of a process. We can model an fNIRS time series using a general non-linear state-space model:

$$x(k) = F[x(k-1), w] + Bv(k)$$

$$y(k) = Cx(k) + n(k)$$

where $y(k)$ is the target time series and the aim is to estimate $x(k)$. Since the present purpose is to estimate the model parameters related to the non-linear function F, only the process equation (2) is considered. Both noise processes $v(k)$ and $n(k)$ are white, zero mean and Gaussian. At each time point, previous state estimates and weight estimates are fed to both of the Kalman filters. Both predictors are then corrected on the basis of observed data $y(k)$, such that they yield current state and weight estimates. By using two Kalman filters working in parallel with one another, we can estimate both state and model parameters of the system at each point in the time series. After estimating the time-dependent MVAR coefficients, the next step is to use those coefficients for the calculation of causality within the time series. By calculating the time-dependent MVAR coefficients at each time point, PDC, based on the principle of Granger causality can be computed. Then, the Fourier transform of these coefficients and PDC can be calculated using the formula:

$$\left|\pi_{i\leftarrow j}(\lambda)\right| = \frac{\left|A_{ij}(\lambda)\right|}{\sqrt{\sum k\left|A_{kj}(\lambda)\right|^2}}$$

where $A_{ij}(\lambda)$ is the $i,j - th$ element of $A(\lambda)$. Then the PDC values follow normalisation properties such as:

$$0 \le \left|\pi_{ij}(\lambda)\right|^2 \le 1$$

By calculating PDC at each time point, multiple matrices corresponding to the time-frequency causality from two time series are obtained. All possible connections between channels (n = 18) were analysed and resulted in 306 connections for each subject. In fMRI and NIRS time series, the frequency band of interest is [0.009-0.08] because it reflects the neurovascular coupling frequency band (Ferrari & Quaresima, 2012; Scholkmann et al., 2014). We thus extracted this mean

frequency band of interest for each connections matrix.

2.6 Statistical analysis

The stationarity of the time series was tested using an augmented Dickey-Fuller test in which it is defined if the absolute solution of the so-called characteristic equation is greater than unity (Halim & Bisono, 2008). Since the PDC's measures have a non-linear relation to the time series data from which they are derived, testing for significance can be difficult to perform. To deal with this issue, after the TPDC values had been estimated, the significance level was calculated from the applied data using a bootstrapping method (Korzeniewska et al., 2003). In short, the original time series of length *(n)* is divided into *(k)* smaller non-overlapping windows of length *υ (n = kυ)*. The order of these windows is randomly shuffled to form a bootstrap sample of the original time series. Then, the MVAR model is fitted to the shuffled time series, and the TPDC value can be estimated. The process is repeated 1,000 times. The TPDC value for each of these 1,000 random permutations is estimated and the 95th percentile TPDC value is taken as the significance level. This process is performed separately for each subject. The resulting value is retained as the significance threshold value for all connections. The significance of the causal measures evaluated from the actual data can be assessed on this basis. In this study the open source Matlab package autoregressive fit (ARFIT) (Schneider & Neumaier, 2001), which allows for modelling and analysing multivariate time series, was used for estimating the AR coefficients from the spatially filtered source signals.

We extracted the mean and standard deviation (std) of TPDC values during the finger-tapping task (6 minutes) to compare the connectivity strength and variability for each connections. Then we calculated the Shannon entropy (E) of the TPDC time series (wentropy Matlab function), to assess the diversity, or uncertainty of each connection's strengths.

For all variables (mean, std and E) we checked the normality of the data using the Shapiro-Wilk test. A one-way ANOVA was then performed (Statistica 7.1) to compare among connections (n=14 after Bootstrapping) (p = 0.05). In case of a significant difference, we performed post-hoc Bonferroni correction.

3. Results

The result of the TPDC analysis is a time-frequency matrix for each connection reflecting the strength of the information exchange. We extracted our frequency band of interest and averaged the matrix in the frequency space to obtain a single time series reflecting the time evolution for each connection (Figure 4C).

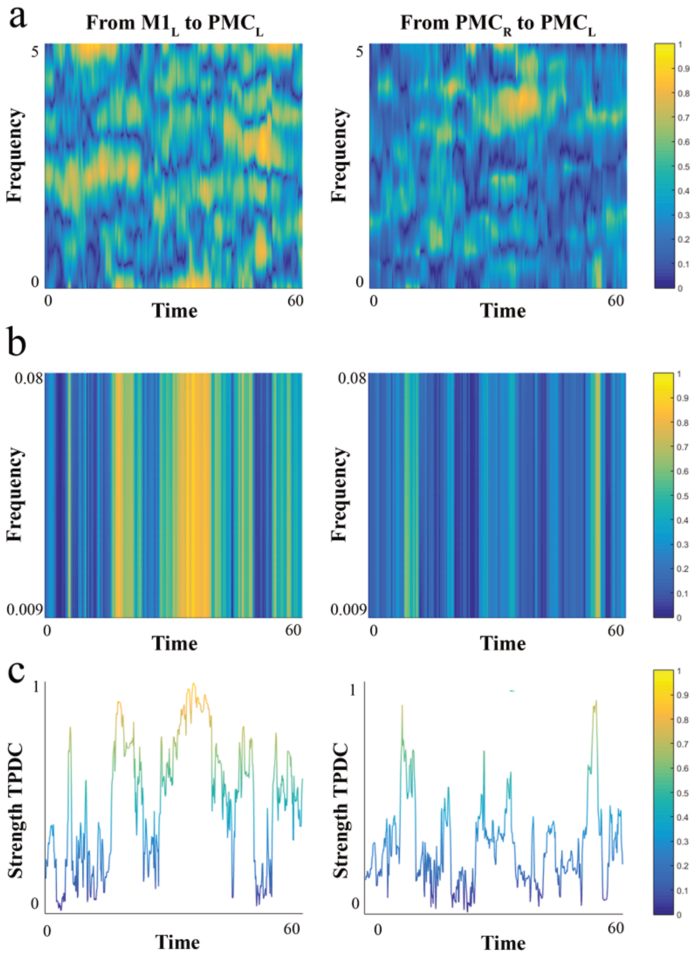


Figure 4C: Example of time-frequency plots generated by TPDC analysis during 60 seconds of the finger-tapping task for 2 connections (From $M1_L$ to PMC_L and PMC_R to PMC_L. a) Time frequency plot for the whole frequency band (5 Hertz). X-axis represents time in seconds Y-axis the frequency in Hertz. Color bars represent the normalised (0 to 1) coherence of the connectivity extracted from TPDC results (blue close to zero connection and yellow close to 1 representing strong connection). b) Time frequency plot for the frequency band of interest [0.009 to 0.08 Hz]. c) Mean of the frequency band of interest. Y-axis represents strength of connection. This example shows higher connectivity strength from $M1_L$ to PMC_L compared to PMC_R to PMC_L.

All the time series were deemed stationary, as we did not detect any unit root. A total of 14 connections (at the whole group level) out of 306 survived the data-driven surrogate ($p < 0.05$). The whole surviving network with the directed connections is shown in Figure 4D. 12 of 14 connections were normally distributed for the mean and 13 of 14 for std and E. Of the significant connections, four were unidirectional connections and five were bi-directional.

The unidirectional connections, namely $M1_L$ to PMC_L, PMC_L to $DLPFC_L$, PMC_L to PFC_L and SMA_L to $M1_L$, were intra-hemispheric and located on the contralateral side to the tapping finger (right hand). The bi-directional connections were all inter-hemispheric between $DLPFC_L$ - $DLPFC_R$, OFC_L - OFC_R, PMC_L - PMC_R, SMA_L - SMA_R and $M1_L$ - M1.

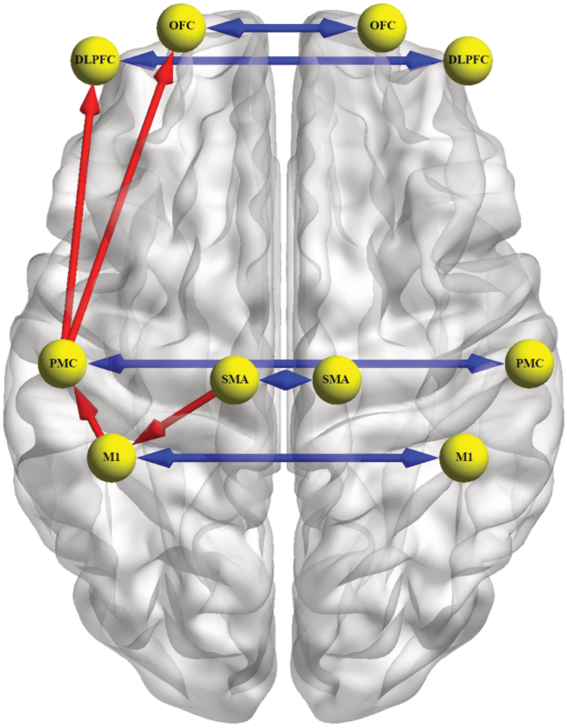


Figure 4D: Whole-surviving connections after bootstrapping analysis (n=14). In blue, bi-directional connections (inter-hemispheric) and in red uni-directional connections located only in the contralateral hemisphere.

The ANOVA revealed significant differences in mean TPDC values between connections $M1_L$ to PMC_L and PMC_R to PMC_L, compared to OFC_L to OFC_R, and PMC_R to PMC_L compared to bi-directional OFC and PFC connections (Figure 4E).

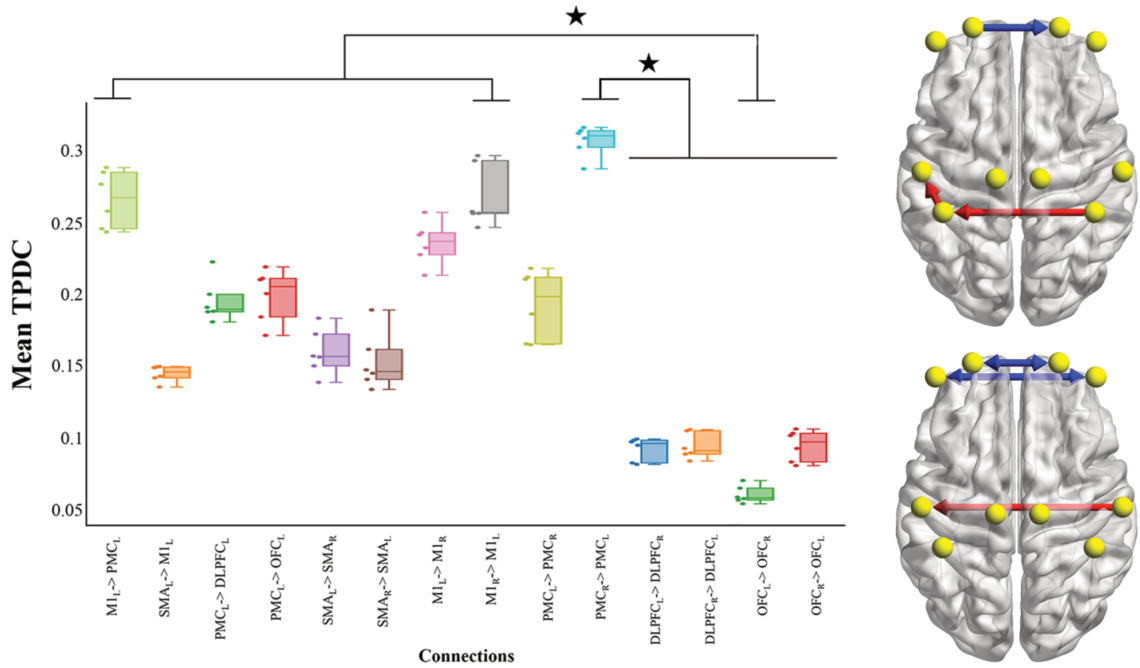


Figure 4E: Average of the TPDC results with Box-plot, individual values and brain representation. Box-plot reflects median, quartile and dots of individuals values for each subject. X-axis represents connections. Y-axis is the mean TPDC value. Stars indicated Anova statistical significance at $p = 0.05$. On the left, representation of statistical significance on brain surfaces (differences are represented between red and blue connections).

For the std and the Entropy of TPDC values, the analysis showed a statistical difference between PMC_R to PMC_L, $M1_R$ to $M1_L$ and $M1_L$ to PMC_L compared to bi-directional OFC and PFC connections and between $M1_L$ to $M1_R$ compare to OFC_L to OFC_R (Figure 4F).

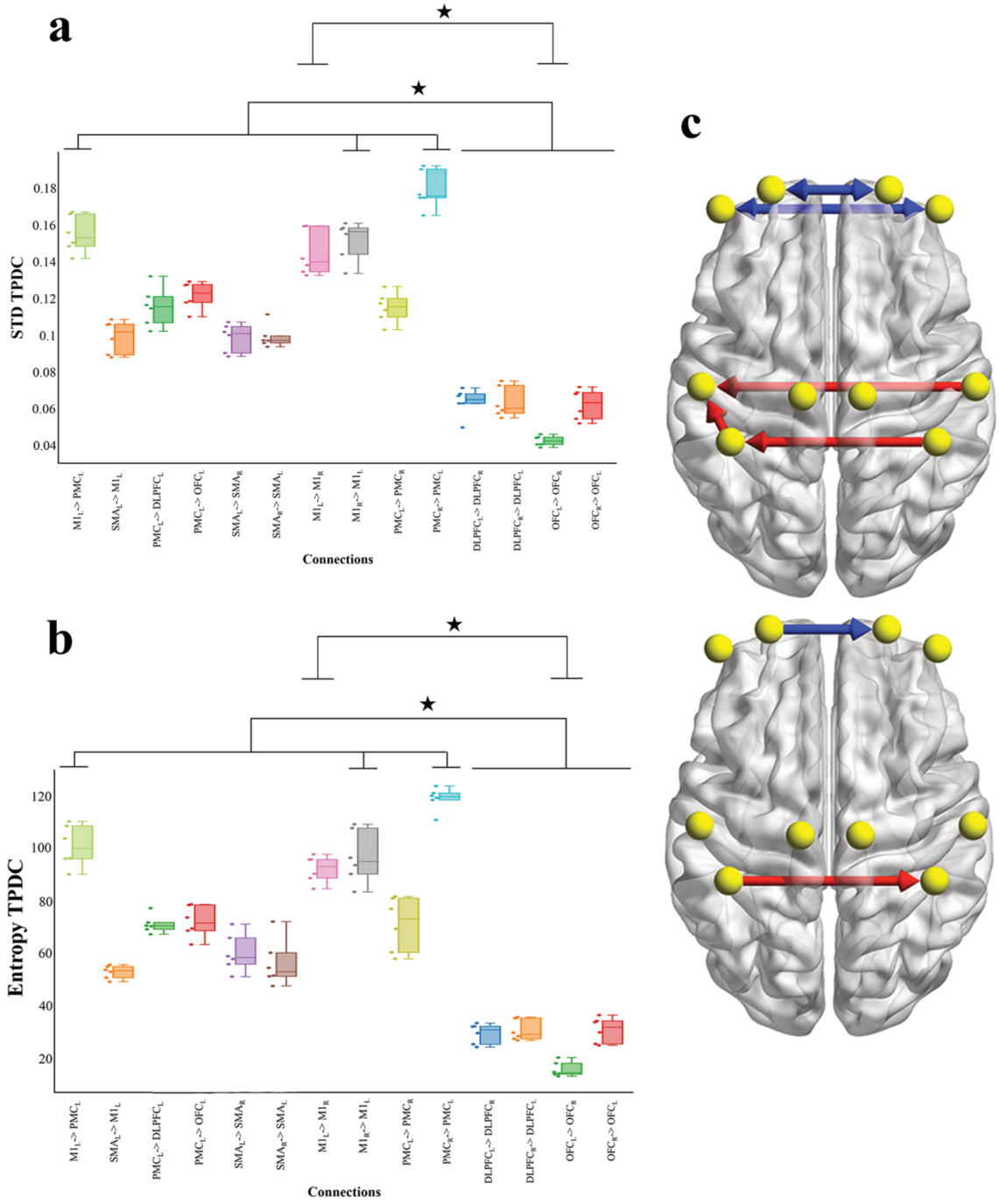


Figure 4F: Standard deviation and entropy of the TPDC results with Box-plot, individual values and brain representation. a) and b) Box-plot reflects median, quartile and dots of individuals values for each subject. X-axis represents connections. Stars indicated Anova statistical significance at $p = 0.05$. a) STD TPDCS. b) Entropy TPDC. c) Representation for both STD and Entropy of statistical significance on brain surfaces (differences are represented between red and blue connections).

4. Discussion

In the present study we focused on the mathematical approach to a time-frequency effective connectivity analysis applied to experimental fNIRS signals. In contrast to other methods currently used in the neuroimaging literature to assess brain network connectivity, the proposed TPDC method provides important insight into the dynamics of connectivity in both the time and frequency domains. Based on an MVAR coefficient assessed by a dual-extended Kalman filtering, this analysis can be used in a number of biological time series (e.g. EEG, MEG, fMRI and fNIRS) to assess the dynamic evolution at rest, for experimental block design as well as during prolonged cognitive and/or motor task performance. Here, we applied this method on real fNIRS data from bi-hemispheric DLPFC, OFC, PMC, SMA and M1 areas (18 channels) during a simple continuous finger-tapping task.

After correcting or disregarding noisy fNIRS signals, we applied TPDC analysis onto the time series of HbO concentration signals and extracted the dynamic effective connectivity and its temporal evolution on our frequency band of interest (i.e., neurovascular coupling [0.009 to 0.08 Hz] (Ferrari & Quaresima, 2012; Scholkmann et al., 2010). The significance testing of our possible 306 connections was performed at the end of the processing using a bootstrapping method: 14 connections survived after running the dedicated analyses. The advantage of the TPDC compared to other connectivity methods proposed in the literature is its ability to assess not only the mean connectivity during the whole time series but also its dynamics, which is of major interest for a better understanding of the brain's dynamic functional (re)organisation.

The lagged-correlation based effective connectivity methods (e.g. GCM) have been extensively used in neuroscience to shed light on directional functional connectivity of the brain. Being complementary to DCM, GCM methods are not based on pre-assumption about the brain, hence increasing their potential applications in many fields. Studies addressing the problem of viability for using GCM on fMRI data claims that this technique is appropriate and a robust measure for fMRI (Wen et al., 2013). This can also be relevant to fNIRS since this neuroimaging technique also reflects hemodynamic changes and relies on the neurovascular coupling in the brain (Logothetis & Wandell, 2004).

Results from the present example

application highlight the fluctuations of connectivity patterns between distant cortical areas, reflected by high std and Entropy results for some specific connections (Fig. 6a c and 6b). First, TPDC shows that there was higher connection's strength over the sensorimotor areas than PFC regions. Then we show high dynamics in all connection's during the motor task revealed by std and E results with higher fluctuations in $M1_L$ to PMC_L, PMC_R to PMC_L, $M1_L$ to $M1_R$ compared to the four connections over the PFC. We also show a higher entropy of TPDC values in $M1_L$ to $M1_R$ compared to OFC_L to OFC_R. Within the context of the present study, our results (std and E) suggest that the effective connectivity evolves dynamically in time.

The network of effective connectivity between cortical regions of interest (ROIs), namely sensorimotor cortex (SMC), PMC, DLPFC, during a finger tapping task in healthy subjects has been presented in earlier studies using MEG or EEG source analysis [18,70]. The GCM analysis has also been applied to fNIRS data to determine the effective connectivity between cortical ROIs in animal and human (Bajaj et al., 2014; Im et al., 2010; Yuan, 2013) experiments. In the above-mentioned studies, simultaneous use of one or two neuroimaging modalities has shown bi-directional or uni-directional information flow patterns between the SMC, PMC and DLPFC ROIs. Recently, by combining fNIRS, EEG and fMRI neuroimaging methods, the effective connectivity of the same cortico-cortical sensorimotor networks (SMC, PMC, and DLPFC) during different finger movement tasks has been revealed (Anwar et al., 2016). However, none of the above studies has looked into the dynamics of the significant connections during the task, between the three ROIs.

Additionally, in the present study we have also included two more important regions involved in motor tasks, the SMA and OFC, assessed in the literature both in activation and connectivity studies [4,14]. We were also able to look at the dynamic inter-hemispheric connections during a unilateral hand movement task, whose the importance of interhemispheric connections by using EEG coherence is known during such a task (Serrien, 2008). Our study highlights a low variability (std and entropy) of bi-directional connectivity in the frontal cortex during a simple prolonged motor task. The PFC being defined as one key anatomical region involved in cognitive processes (Dreher & Berman, 2002) leads us to conclude that our present task does not seem to require a high implication at the cognitive level (low

TPDC strength in OFC and DLPFC areas (cf. Fig. 5)). At the sensorimotor level, observing high bi-directional connectivity strengths (Fig. 5) between both hemispheres seems consistent with the literature: First, it is well known that there are high bi-hemispheric functional connections for multiple sensorimotor areas at rest and during a motor task (Thompson & Fransson, 2015; Biswal et al., 1995). Second, our subjects performed a uni-manual motor task, of which the contralateral motor network is known to be primarily involved (Bajaj et al., 2014).

The functional network of cortical ROIs involved in rhythmic and sequential finger movements in healthy subjects has been analysed using EEG (Muthuraman et al., 2012), MEG (Pollok et al., 2006), fMRI (Nedelko et al., 2010) and fNIRS (Leff et al., 2011) separately, and the SMC, PMC and DLPFC have been found to be the three core regions of the cortical sensorimotor network for movement control (Witt et al., 2008). Using TPDC method, our present findings allow extending a previous fNIRS study that showed only bi-directional effective connectivity in the contralateral hemisphere between SMC and PMC during performance of a hand motor task (Bajaj et al., 2014). The directions of information flow for rhythmic movements in earlier studies have shown that the SMC plays a major role in directing voluntary motor tasks (Anwar et al., 2013). Nevertheless in this previous study, authors analysed only the mean of connectivity strength and don't take into account the dynamic of the network during the task. Since one of the key properties of the brain is the continuous juggling between functional integration and segregation, our results emphasise dynamic changes over short time windows (Fig. 3c) in the configuration of brain connections.

5. Methodological considerations and limitations

5.1 Pre-processing of fNIRS data

Movement artefact is known to be one of the biggest causes of spurious connectivity analysis. In this study we used a combined artefact deletion technique (Spline interpolation and wavelet). While we used this combined pre-processing approach with parameters proposed in the literature (Scholkmann et al., 2010; Molavi & Dumont, 2012; Cooper et al., 2012), the potential effect of a few undetected artefacts, or the effect of some signal transformation due to the correction on causality analysis, remain however to be clarified. More generally, discriminating between a 'good' and a 'bad' channel in the analysis of fNIRS time series is still an unsolved methodological issue. While it

seems quite easy to discriminate between very noisy or not noisy signals, several other characteristics of the signal need to be carefully taken into account to determine which fNIRS signals are suitable for subsequent analyses. A comprehensive investigation of the different fNIRS pre-processing methods, including use of simulated data with multiple levels of noise and real fNIRS data from different experiments, probe positions and systems of data collection, would be very valuable in the aim of developing a unified procedure to select physiologically relevant fNIRS signals.

5.2 Time partial directed coherence

Despite the advantages of using TPDC over conventional causality methods, one drawback is that the TPDC method is time-consuming, owing to the estimation of MVAR coefficients at each time point. This limits its usage depending on the available computational resources and is not appropriated for fast diagnosis. It is important to point out the fact that the Granger Causality approach was used in this study to measure the brain dynamics inherent to a finger-tapping task, the interplay between segregation and integration, and not to study the underlying mechanism involved in this particular motor task. Our connectivity results are dependant on the targeted cortical areas and need to be considered within the limitation of the spatial resolution of fNIRS.

Due to its poor spatial resolution but relatively high sampling frequency, fNIRS is a promising tool to investigate the dynamic connectivity of the cortex, but appears a limited tool to realise a mapping of connectivity for the whole brain. Nevertheless, some recent studies highlight the importance of these dynamics or fluctuations in the brain more than the localisation of the static connectivity between brain areas (mapping). One of the important developments needed to improve the TPDC method is to investigate the functional properties of these multiple networks with more appropriate tools. Furthermore, we analysed the mean of the dynamics during the entire motor task and do not take into account the global network properties. A graph analysis approach could be one way to extract the functional properties of TPDC results combining each connection in the same time. In addition, to specifying which parts of the brain are connected to others, graph analysis could help our understanding of the functional organisation such as integration, segregation or small world network organisation. Nevertheless, few fNIRS studies have investigated this kind of analysis up until now and refer to another

level of abstraction for the comprehension of the data (Fallani et al., 2014).

6. Conclusion

This study proposed TPDC as a new time frequency effective connectivity analysis to be applied to fNIRS signals over multiple bi-hemispheric brain areas (M1, PMC, SMA, OFC and DLPFC) to investigate the time dynamics of the brain network during a continuous finger-tapping task. The present contribution allows us to specify the direction of the link between two regions of interest: indeed, four connections (SMA_L to $M1_L$, $M1_L$ to PMC_L, PMC_L to $DLPFC_L$ and PMC_L to OFC_L) have been shown to be unidirectional and five are bi-directional connections, information that would typically be concealed using common functional undirected connectivity methods like correlation or coherence. Characterising the dynamics of brain network configurations could allow discriminating between healthy subjects and patients showing altered brain dynamics. TPDC could, for instance, be used to investigate the lesion effect of one brain area due to stroke, and the brain plasticity phenomena associated with functional motor recovery during the acute phase after stroke.

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Disclosures

The authors declare no conflicts of interest, financial or otherwise.

Chapter 5

General discussion and perspectives

For more than twenty years, there has been a craze in the human movement sciences for the analysis of biological time as diagnostic tools in different states such as disease or fatigue. In particular, the pioneering work of Hausdorff set the stage for hope when discovering a relatively simple tool to discriminate healthy participants from elderly or pathological subjects. These hopes, although generally evidenced by an accumulation of empirical approaches, find their basis in many publications investigating a large number of pathologies. Nevertheless, developed in parallel and outside any clinical or pathological context, some authors have also showed that such an analysis can be sensitive to the experimental conditions set up by the researchers, especially by modifying the constraints imposed on the subjects.

Although these two approaches may seem contradictory, there is a possible confounding factor that has not been studied until today to our knowledge. This factor is at the centre of the reflections and works carried out during this dissertation, particularly in our first study (see Chapter 2). Although a single study is not in itself generalizable and requires further validation in the future, our work opens many avenues for reflections that we will develop later in this chapter in Section 5.1. Following these first preliminary results obtained, several ways opened and we decided to guide our work on the concept of degeneracy and in particular the possible link between long-range correlation analyzes of motor output time series with the cortical activations involved during the experimental sensorimotor paradigm proposed (see Chapter 3). This second study opens promising new directions of investigation but suffer from certain limitations that are developed in Section 5.2. These limitations however can be relatively easily tested by specific work answering these shadows. Finally, this work allows to propose new scientific questions, which are exposed in Section 5.3 and which would require considerable but stimulating deepening in future works.

5.1 Functional significance of fractal properties

After a brief review of the main results obtained in the study presented in Chapter 2 of this dissertation, we will analyze in a critical way the limits that these works highlight as well as the future follow-up that these works allow us to hope for. The finding of two factors inducing a loss of complexity, expressed through potentially confounding fractal analyzes in the literature, has often led studies to voluntarily move towards one or the other possible explanation. Nevertheless, although empirical evidence abounds in these two explanations, which are the loss of complexity with aging or disease on the one hand, and the loss of

complexity due to increased sensorimotor control on the other hand, no study to our knowledge has attempted to reconcile and directly question these two types of approaches directly. Using a relatively simple but robust experimental paradigm (finger-tapping task) which has been the subject of many studies, we were able to control our experimental conditions while limiting as much as possible the effect of multiple other factors that could "add noise" in our results, such as fatigue, weariness or modification of unwanted variables in our paradigm. We made three hypotheses regarding the effect of suppressing of different feedbacks in performing this motor task as well as depending on the analytical method used and the population studied. As a reminder, these assumptions were: (i) healthy subjects performing a simple finger tapping task reflect a same mono-fractal exponent regardless of the external constraints imposed the task performance, (ii) multi-fractality evolves with the external constraints, auditory, visual or tactile feedback imposed to the task performance and (iii) the loss of the proprioception feedback (in the deafferented subject and groups deprived of proprioception) reflects a decrease in all behavioral variables (performance, mono-fractal and multi-fractal) as compared to other groups.

Our results are based on 94 healthy subjects and one deafferented patient (IW) shared in eight conditions: control, -1 FB (auditory or visual or proprioception), - 2 FB (auditory and visual, visual and proprioception or auditory and proprioception) and - 3 FB (auditory, visual and proprioception). Our preliminary and expected results showed a decrease in the α-DFA exponent for IW compared to the other experimental groups. In addition, the extracted multi-fractal variable (MF-Width) increased with the number of feedbacks deprived. The results of our first study allow differentiating the functional significance of mono- and multi-fractal analyzes, which are generally considered to be only for the second a finer-grained analysis than the first (Kantelhardt et al., 2002; Ihlen, 2012). Indeed, the mono-fractal analysis discriminates only groups with proprioception deprived and IW compared to other conditions (groups). This suggests that the α exponent could indicate the constraints imposed to the system as reflected by a reduction of the alpha exponent in conjunction with a decrease in level of performance during the task. Long-range correlations in the inter-tap intervals remain present until the constraint (external in our case) imposed on the subjects becomes too strong. This was also reflected in a decrease of performance. Nevertheless these findings, question in particular the original results proposed by Hausdorff et al. (1997) for a walking task. Indeed, these authors have studied the evolution of long-range correlations between successive step in healthy subjects, elderly and suffering from Huntington's disease. Although these authors

showed a decrease in mono-fractal exponents with age and pathology compared to healthy participants, the extracted performance variables such as step amplitude and coefficient of variation are not statistically different between healthy young and old subjects. In contrast, the coefficient of variation was significantly different in patients with Huntington's disease compared to the control group. If we are interested in the mono-fractal exponent, the older subjects had an average alpha of 0.68 while the patients had an alpha of 0.60. These results raise the question of a possible distinction between healthy subjects on the one hand and subjects suffering from a pathology on the other. This is particularly critical in the possible progressive evolution of the advance in age or the worsening of the pathology. Long-range correlations could reflect a continuum in the evolution of system degeneration to such an extent that effective adaptation to the task would no longer be possible at all (e.g. inability to walk for example) and would therefore be a means of predicting the evolution of systems. Longitudinal follow-up studies on cohorts of elderly subjects or those with evolutionary pathologies would provide a better understanding of the changes of mono-fractal properties.

On the other hand, we found thaht the width of the multi-fractal spectrum (MF-Width) increased with the number of feedbacks removed. These results assume that multi-fractal analyzes reflect the dynamic of multiple sub-systems involved to perform the task at multiple time scales (Ihlen & Vereijken, 2010, 2013; Kutznetsov & Wallot, 2011; Stephen & Dixon, 2011). These fluctuations can be understood as a multiplicative cascade process that has been suggested as the underlying property to self-organization and metastability of systems to achieve performance (Turvey 2007, Van Orden et al., 2003). Nevertheless, our experimental paradigm allowed us to highlight changes in multi-fractal properties based on the number of feedback participants were deprived of but not on change in performance. We have proposed in this dissertation that the concept of degenerecy can be the keystone of the evolution of multi-fractal properties under different constraints. Degeneracy does not seem to be antinomic here when approaching the multiplicative cascade dynamics. Degeneracy could be reflected at all scales in the system and more or less intermittently, which would allow the system to adapt to the surrounding conditions (Ihlen & Vereijken, 2013). The increase in the width of the multi-fractal spectrum in our studies suggests that under an increasing level of “constraints”, the subject will use more degenerate sub-networks (or sub-systems) to maintain the performance in the task as much as possible.

The opportunity we had to include one deafferented participant and the results obtained by this single subject compared to other experimental groups bring many questions. Indeed, the increase in the variability of (proven) tapping series with regard to analyzes such as the coefficient of variation in IW and groups without proprioception are in compliance with studies carried out on the suppression of proprioception for this kind of experimental paradigm (Stenneken et al., 2002). The proprioceptive feedback would be the most important sensory modality in the realization of a rhythmic task such as finger tapping to maintain a level of performance. On the other hand, the differences obtained (Figure 2B) in the mono-fractal DFA and multif-ractal MFDFA analyzes question even more. A decrease of performance was expected with the suppression of the proprioception due to a lesser inability to adapt. Nevertheless, the joint evolution of the coefficient of variation and the alpha DFA exponent are resulting from the time series produced by IW puts questions. With this deafferented subject, we had the opportunity to test initially the effect of the suppression of proprioception (while waiting the ongoing results with the anesthetic block in healthy participants). The increase in the CV seems consistent with our hypothesis that performance should be degraded without this feedback. Nevertheless, the DFA analysis does not make it clear that it could reflect the adaptability of the system. IW is older than other recruited subjects and therefore, long-range correlations close to white noise could be due to this factor (Hausdorff et al., 1997; Amoud et al., 2007). Thus, the results of the Study 1 remain on a questioning about the meaning of the mono-fractal properties.

In addition, the multi-fractal analyzes show a gradual increase in the widths of MF-Width spectra as a function of the number of feedbacks suppressed (Figure 2B). Although this result could give more confidence in the expected effect of proprioception, we need to be cautious about the interpretations of these results, particularly with regard to the literature that has had the opportunity to study these pathological populations (IW) under many experimental conditions. Indeed, it has been shown that such patients have at least partially adapted to their pathology to achieve as much as possible activities of everyday life. These compensatory strategies over time could therefore lead to a confounding factor in the effect of proprioception for the accomplishment of our task (Bernier et al., 2006).

Following a relatively logical sequence to these questions and in the interests of completing the study, the suppression of sensory feedback such as proprioception should be carried out in subjects whose age corresponds to that of our deafferented participant. A first

possibility already exploited in the literature would be to create a nerve stimulation to prevent "correct" proprioceptive feedback (Pipereit et al., 2006). Nevertheless, such stimulation could create a disruptive sensory feedback (noisiness), which would provide the brain with false information and therefore would not be in direct adequacy with the mere suppression of sensory information. A second possibility that we had initiated during this study (results in progress) is to create a sensory anaesthetic nerve block to allow subjects to maintain motor control without having tactile and proprioceptive sensory feedbacks. This sensory block makes it possible to test the effect of the suppression of proprioception alone in healthy subjects, but also the different combinations of sensory modalities and number of feedbacks.

Finally, a fundamental question arises as to the evolution over time of these fractal properties. Indeed, no studies to our knowledge have currently studied the evolution of the systems questioning the possibility of a continuum progressive increase or decrease in complexity during life or a possibly abrupt transition from a complex system (adaptable) to a system that relatively suddenly would not be (Figure 5A). This is all the more so since previous studies generally investigate neurological or advanced age pathologies that lead to a relatively slow decline. The advancement in age can hardly be conceived as a binary (or bistable) approach, classifying individuals as young or old. The approach currently used in our work suggests, especially through the concept of degeneracy, a relatively brutal transition. In fact, theoretical work and simulations suggest a minimum number of degenerate networks necessary to adapt a complex system (Price & Friston, 2002, Delignières & Marmelat, 2013). We would then have to find out an experimental paradigm (e.g. animal model and/or computerized simulations) allowing to suppress sensory feedbacks in a progressive way or to study the longitudinal follow-up of relatively large cohorts.

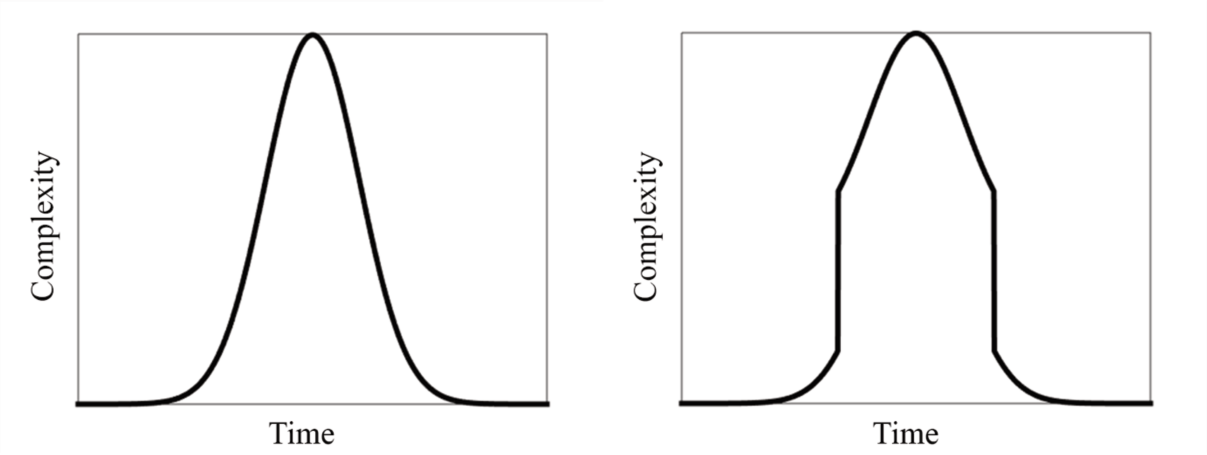

Figure 5A: The two proposed potential time courses of the loss of complexity. Left: continuous increase and then decrease of complexity. Right: shift at a given time between low complexity and high complexity.

5.2 A possible link between motor variability and the dynamics of cortical networks

In a similar way to the previous part, we will recall here the results obtained in the Study 2 presented in the Chapter 3 attempting to make the link between the sensorimotor variability and the dynamics of brain networks before highlighting the methodological limitations of this study as well as its possible evolutions. In this second study, based on the same experimental paradigm (finger-tapping task) as the previous one, we tried to prove the link between the multi-fractal properties of the inter-tap interval and the distribution of cortical networks studied by the fNIRS method. We hypothesized that the variety and intermittency of the brain networks involved in the task and the fractal properties of tapping series evolve jointly according to the different feedback deprivation conditions.

The main results showed a correlation between the width of the multi-fractal spectrum and the number of networks involved during the task. Although this study has some limitations due in particular to the methodological concerns inherent to fNIRS method, this study is the first to our knowledge, to attempt to establish a direct (experimental) link between the fractal properties of the motor control and the cortical networks using a promising neuroimaging method. This study reinforces the idea that multi-fractal analyzes would reflect the effective adaptations made during the task. The elimination of an increasing number of feedbacks would require the involvement of more brain networks and greater intermittency to maintain the required level of performance.

Although our work focused here on the study of the effective adaptations of healthy subjects in a relatively simple experimental motor paradigm (finger tapping), there is a questioning in particular with regard to the work initiated by Whitacre (2010). Indeed, according to this author, degeneracy is the central property allowing to connect complexity, robustness and evolvability (Figure 5B).

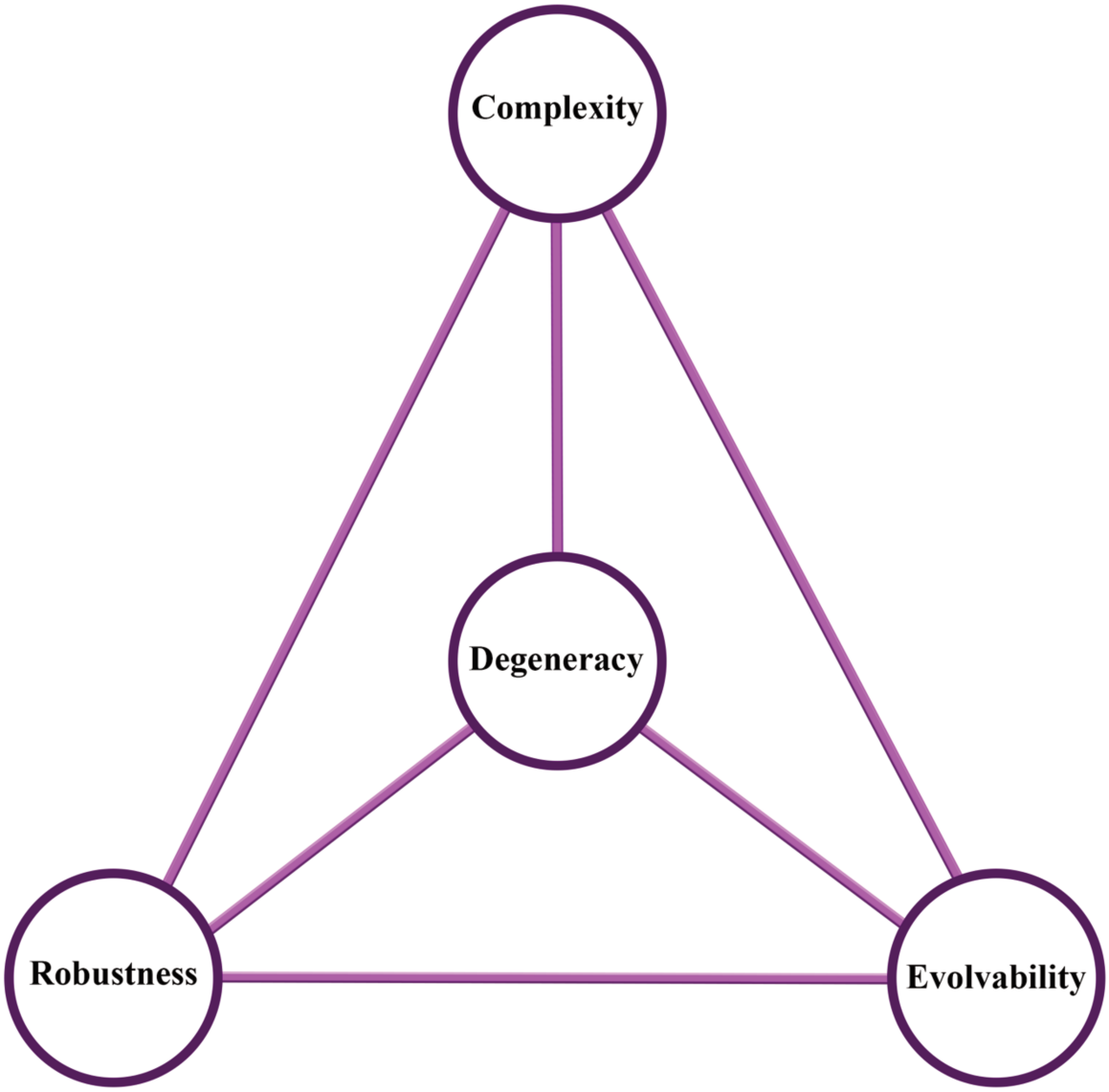

Figure 5B: The triptych between complexity, robustness and evolvability. Degeneracy is the cornerstone between these three properties of biological systems. Degeneracy is source of robustness, increases evolvability and is correlated with complexity (adapted from Whitacre & Bender, 2010).

In our previous two studies, we tied with the proposed experimental paradigm to de-correlate the fractal properties of performance measures such as mean and coefficient of variation. This approach made it possible to study the link between degeneracy and some forms of robustness in the face of changing experimental conditions (the number of feedback we are deprived of). Nevertheless, to fully study the degeneracy of a system, we should also be able to test this evolvability capacity. Evolvability can be seen as the ability of a system to change or create innovation to meet a demand (internal or external). In this sense, the joint study of the fractal properties of behavior with the dynamics of the cortical networks involved in a learning process seems relevant (since evolution in the Darwinian sense seems difficult to achieve from an experimental point of view). Recent studies have been initiated in this direction at the level of the motor control (e.g. Nourrit-Lucas et al., 2015). On the other hand, the work carried out by Bassett et al. (2011) in fMRI is promising in particular to answer our current scientific questions at the level of the brain. Indeed, these authors have analyzed the dynamic reorganization of cortical networks using a method initially proposed by Mucha et al. (2010) in a learning paradigm. This "multilayer" method makes it possible, unlike the one we used in the study discussed here, to distinguish module changes from nodes over time (i.e. before, during and after learning), as well as their dynamics. Their results show an increase in the dynamic modular changes at the beginning of learning and a decrease at the end of learning. In addition, this variable seems to be a good indicator of learning potential, especially by comparing the first learning session versus the second session. These promising results could be applied jointly to fractal behavioral analyzes as performed in our laboratory to better understand the link between evolvability and degeneracy.

The work presented in this dissertation is relatively fundamental and may suffer from a possible lack of direct links between the results obtained, which are certainly promising, and their possible applications in "real life", particularly in the field of clinical applications. The results obtained in our first two studies as well as the possible avenues put forward above in the context of the learning allow to open a possible field of application of the theoretical questions initiated in this dissertation particularly in rehabilitation physical medicine, with a focus on patients who have suffered a stroke. Stroke remains a major public health problem today, being the leading cause of acquired disability in adults. Considering the prognosis of functional recovery of the upper limb, only 10% of patients fully use their upper limb (Kwakkel & Kollen, 2013). Although many clinical studies have focused on the development of new rehabilitation methods or the validation of clinical diagnostic tools (scales), there does

not seem to be a dominant method to date to better anticipate possible recovery after the injury. Early detection of this recovery capacity is necessary, as most motor recovery appears to occur during the first three months, or early in the post-stroke phase. Indeed, the best recovery rate is achieved in 80% of patients at 1 month and 95% of patients at 11 weeks after the stroke date (Jorgensens et al., 1995). Our results suggest that fractal analyzes of sensorimotor tasks at the level of behavior in the early phase of stroke may guide the therapist about the capacities (functional reserves) available to the patient. Moreover, conducting studies on the evolution of these properties in learning paradigms could then make it possible to follow longitudinally the effect of rehabilitation programs with a new score easily implemented and at a lower cost. However, very few studies to our knowledge have attempted to analyze the complexity of sensorimotor signals from this type of population and generally remain restricted to a walking paradigm (Akay et al., 2004, Mizuike et al., 2009). These longitudinal tracking would make it possible to answer a fundamental question especially with regard to the loss of complexity. Indeed, although the loss of complexity can easily be conceived, one of the most important questions is whether it is possible to restore the complexity of a system that has been damaged.

For their part, studies in neuroimaging are relatively numerous, especially with the use of fMRI, and have provided many responses to brain's post-stroke organization both for activation and functional or effective connectivity. This research works has shown that following a stroke, there is an increase in the activation of many cortical regions to perform a motor task of the paretic member. This is particularly the case for M1, PMC, SMA, parietal and prefrontal cortex, in both hemispheres (Ward et al., 2003, Gerloff et al., 2006). However, these localization studies do not explain how regional activations affect the process across the networks. Studies using functional connectivity have shown changes in interhemispheric connections particularly between similar areas of both hemispheres (Carter et al., 2010, Park et al., 2011). Disturbed interhemispheric connectivity of ipsilesional M1 was also reported for contralateral connections to PMC and posterior parietal cortex (Wang et al., 2010). Furthermore, the main finding of effective connectivity in stroke patients showed a reduced intrahemispheric connectivity in the ipsilesional hemisphere (Grefkes et al., 2008, 2011). Although the analysis of connections between cortical areas provides new information about the severity of stroke and a good prognosis of the level of recovery, the theoretical explanation of these changes is still debated in the literature (Rehme & Grefkes, 2013).

More theoretically, early functional recovery following stroke could be understood as a quick recovery from a complex organization of brain connections. This organization can be understood as an optimal balance between a simple and totally rigid network and a totally random and organized network with too many connections (Figure 5C). This optimal scale is understood as a cost-efficiency ratio, one of the essential properties of healthy adaptive subjects (Bullmore & Sporns, 2012). In this sense, there would be optimal degenerate system when performing motor tasks, consisting of a limited number of functional configurations. Too few available networks would not be able to perform the task properly. On the other hand, too many networks involved would reflect high cost and low efficiency. Thus, the study of the dynamics of the networks involved in rehabilitation protocols would reflect the state of the system.

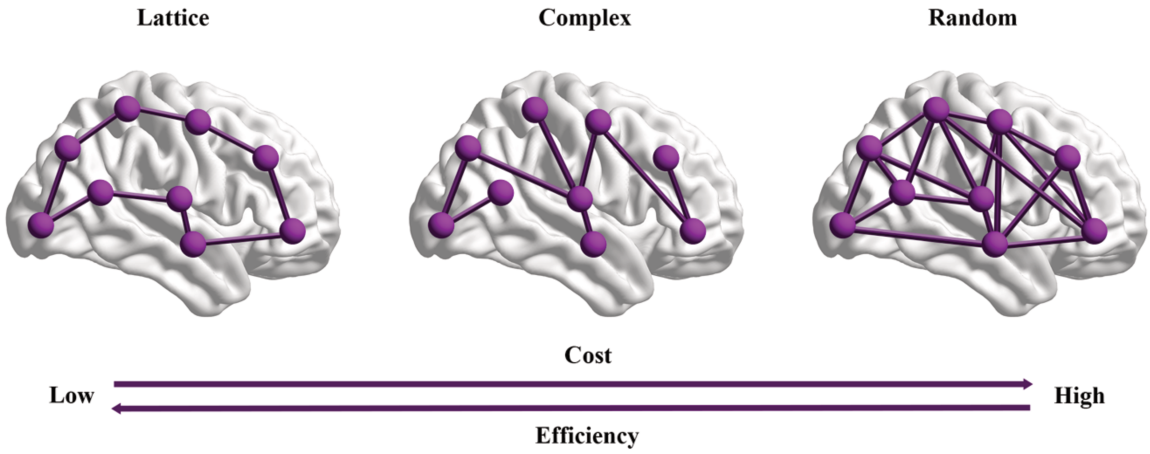

Figure 5C: Optimal brain network organization (adapted from Bullmore & Sporns, 2012). A complex topology is an optimized balance between cost and efficiency. More connections increase the cost of the network. Lower connections minimize the efficiency of the network.

5.3 Directed connectivity in fNIRS

To conclude the discussion of our research work we will move forward on the perspectives following the Study 3 of our dissertation. One of the main limitations of our Study 2 was the use of functional connectivity based on the Pearson correlation coefficient. There are many limitations to the use of this analysis (Hidrinks et al., 2016, Hutchinson et al., 2013) although it is commonly used commonly used. Our first choice was a relatively simple approach, which could be comparable to the literature. Nevertheless, transitivity phenomena and the lack of information on the orientation of the connection link led us to test a recently developed

analytical method called time partial directed coherence (tPDC; Anwar et al., 2013, Muthuraman et al., 2018). This method is particularly promising because it is based on a multivariate auto-regressive modeling and allows the directionality of the link between the cortical areas to be estimated. However, this method is very expensive from a computational point of view and cannot be considered at the moment in a clinical routine or in "real time" analyzes such as with the Brain Computer Interfaces use.

Nevertheless, we must return here to the possible follow-up to this work. Many authors have shown that the analysis of connectivity between different brain areas provides limited information about the functional organization of the system itself (Rubinov & Sporns, 2010, Fallani et al., 2014). The so-called Graph theory approach, one of the branches of mathematics, was recently applied as a result of connectivity analyzes (Figure 5D). These analyzes are generally applied to provide a better understanding of the topological organization of a network, especially in terms of integration and segregation. Numerous properties have thus been highlighted, such as a modular organization (Sporns & Betzel, 2016), hubs (Van Den Heuvel & Sporns, 2013) and small world networks (Bassett & Bullmore, 2006) (See Box 4 for an introduction of these concepts). One of the key questions is whether these analyzes are adapted to the relatively limited spatial resolution proposed with regular fNIRS instrumentation (that is not using diffuse optical tomography). Some initial responses reveal comparable results of effective connectivity between fNIRS, fMRI and EEG (Anwar et al., 2013). Other authors point out that graph analyzes are relatively stable and reproducible with the use of fNIRS (Niu & He, 2014, Geng et al., 2017). However, this experimental evidence was not applied to dynamic directed analysis and is generally limited to the rest paradigm (resting state). Future works using fNIRS is needed with these types of analysis.

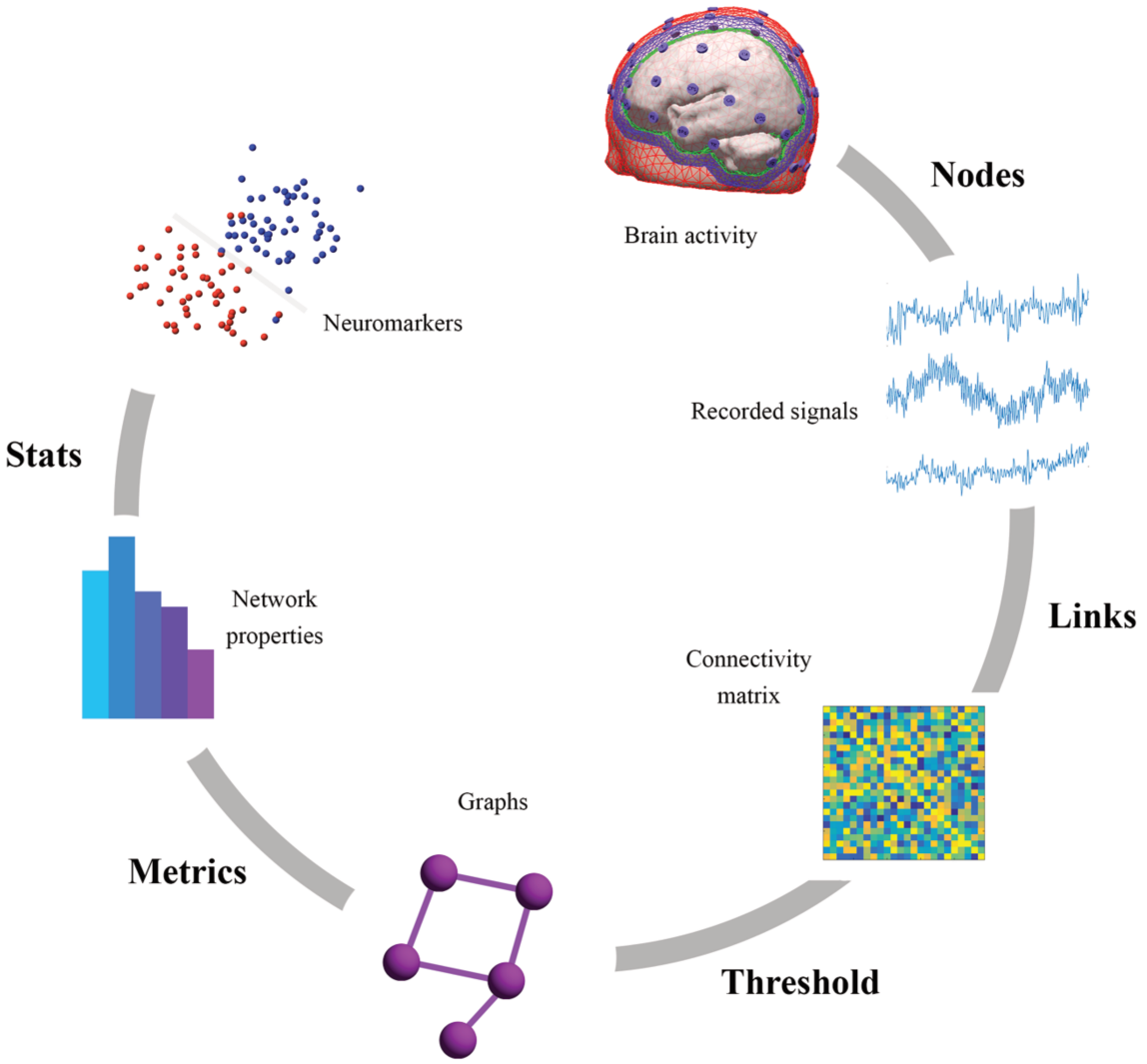

Figure 5D: Schematic representation of the connectivity analysis process in neuroscience (adapted from Fallani et al., 2014). Nodes correspond to fNIRS channels in the present dissertation. Links could be either undirected (correlation) or directed (tPDC). Threshold could be applied or not depending on the Graph analysis used. Metrics are implemented to reflect global, intermediate or local properties. Finally (out of scope of the dissertation) different statistics can be applied.

Finally, although part of the previous discussion focused on a possible use of the research work undertaken in this dissertation for a better understanding of a pathology (stroke), it would seem interesting to also study these types of analyzes on experimental paradigms using non-invasive brain stimulation (e.g. transcranial direct current stimulation,

tDCS). Indeed, tDCS can exert modulatory effects on ongoing neuronal activity and excitability (subthreshold) and, as such, is promising when combined with conventional rehabilitation training programs in stroke (Hummel & Cohen, 2006). Nevertheless, these neuromodulation techniques also modify the connectivity of stimulated networks (Keeser et al., 2011, Polania et al., 2011). The combined use of behavioral and neuroimaging analyzes would make it possible to highlight the possible dynamics changes (intermittency) between the networks as well as their functional properties to better understand the potential effects of tDCS, particularly for clinical purposes.

5.4 Increase the potential of fractal approaches

The ubiquitous character of long-range correlations raises questions when it is potentially useful, particularly as a diagnostic tool. Indeed, the observation of this phenomenon in many fields of research and at many scales of observation of biological variables may limit its use to a single scale. Van Orden et al. (2003, 2005) proposed that knowledge of the composition of the underlying system is not essential for understanding the presence of long-range correlations. On the other hand, Wagenmakers et al. (2005) considered that a better understanding of the properties of the underlying system is necessary to allow a real use of fractal measurements. To know all the components of a system as complex as the human seems impossible at the moment. Especially since it is composed of many different but interrelated elements. Nevertheless, taking into account several layers would allow a better understanding of how the system works. In this dissertation, we first studied the ability of individuals to adapt to a single level of observation (macroscopic) and to a single variable (inter-tap intervals). In our second study, we then tried to establish the link between this variable and the dynamics of brain connections using fNIRS. Nevertheless, to go further and try to better understand the mechanisms of adaptation (or the adaptability potential) of the systems, it is critical, as mentioned above, to couple several approaches (including neuroimaging) at rest but also in the realization of cognitive-motor tasks. Obviously, these different levels of analysis, studied in isolation, without taking into account the links and dynamics that animate them both on their scale but also between scales, would remain reductive.

Recent approaches would allow for a significant breakthrough in this direction and would make it possible to answer theoretical questions often presented, simulated and discussed in

the literature (Wagenmakers et al., 2005, Van Orden et al., 2005, Diniz et al. 2011). Among the key questions that can be asked when the possible origin of long-range correlations arises:

- Are the robustness and adaptive capacity of the system driven by essential/specific nodes?

- On the contrary, is it the opposite? Smaller nodes would play a major role here in the dynamics of system adaptation.

- How does the modification at a given level of certain nodes or edges lead to modifications to another “upper” or “lower” level and at what limit?

- Although many different levels exhibit fractal fluctuations, do the inter-relationships between levels also follow this communication model?

- Finally, is the degeneracy limited to one layer (e.g., neurons) or between layers that make up the system?

These questions could therefore supplement the diagram we have initiated in this thesis (Figure 5E). Nevertheless some of these have been answered partly in recent years years due to the evolution of graph theory. Still considered static and used at a single scale of observation, the topological organization of systems is now studied in the form of multilayers, analyzing their temporal evolution and their multiscale links. This multilayered approach should therefore not to be confused with a large network that will quantify all connections at a single observation level. A multilayered approach will also integrate information of different kinds between observation scales. This approach therefore makes it possible to extract more information about the complex system under study. Despite the fact that this relatively refreshing approach is still in full development and although it is promising, it must be the subject of many studies regarding the possibility of using these analyzes in our field (for the interested reader, two reference works have recently been published recently on this topic: Bianconi, 2018; Garas, 2016).

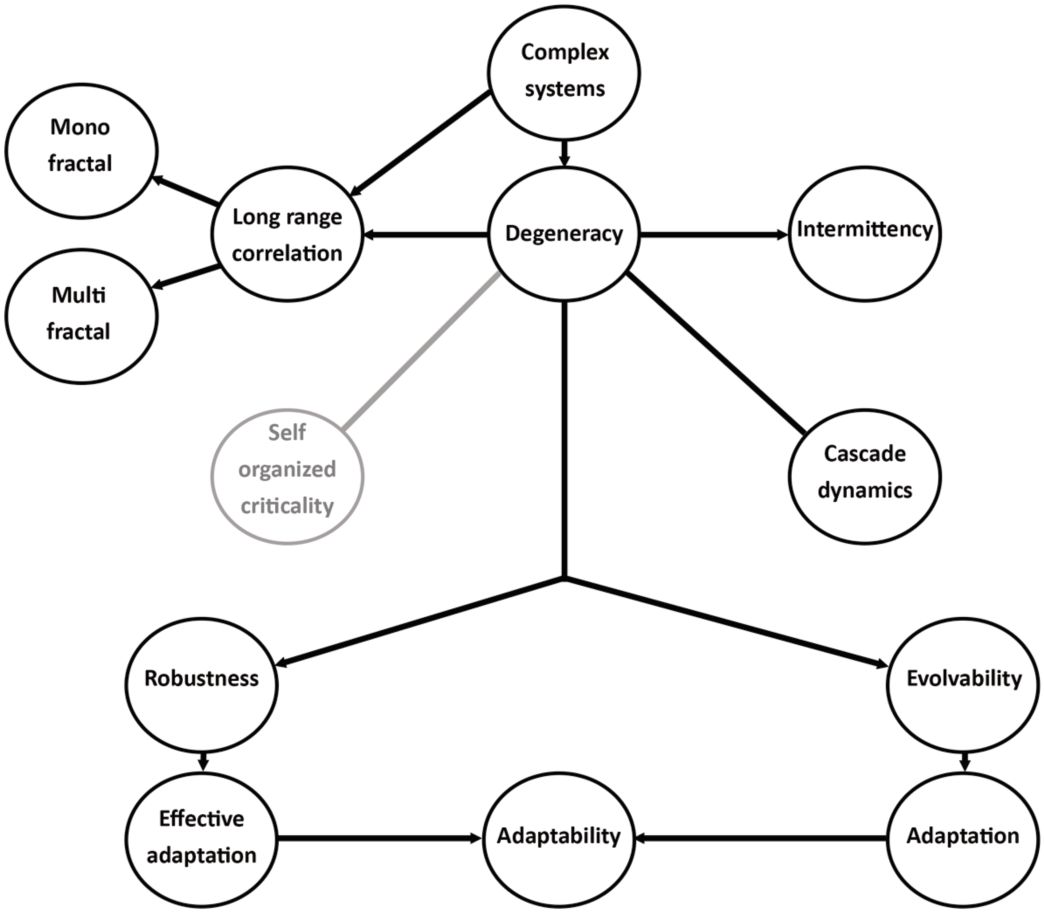

Figure 5E: Diagram representing key words addressed during this dissertation. This diagram will be able to evolve thanks to the continuation of future studies

Box 4

Graph Theory

"By the 20th anniversary of the paper, more than 18,000 papers have cited the model, which is now considered to be one of the benchmark network topologies. Watts and Strogatz closed their paper by saying: "We hope that our work will stimulate further studies of small-world networks." Perhaps no statement has ever been more prophetic."

Vespignani, 2018; On the paper: Watts, D. J. & Strogatz, S. H. *Nature* **393**, 440–442 (1998)

The Graphs theory has its origins in solving a problem concerning the spatial organization of the city of Königsberg. It was in 1735 that the mathematician Léonard Euler proposed a solution to the so-called "seven bridges" problem. This problem arises as follows: go around the city by taking the seven bridges composing it once and only once. The solution proposed by Euler (Figure 5F) results in an abstract visualization of the spatial organization of the city without taking into account the "real" geographic location. This work is considered as the beginnings of mathematical graph theory (Bullmore & Sporns, 2009). From a mathematical point of view, a graph G is composed of nodes (or vertices, V) and edges (connections, E). This graph can be represented graphically (as in the example of Euler, Figure 5F) or by an adjacency matrix or a line (or column) represents a connection between the node X and all the other nodes composing this matrix. For the sake of clarity we will only present examples based on non-directed binary matrices (the connection is considered to be reciprocal between two nodes and its weight will be 0 if the connection does

not exist and 1 if the connection exists). For the reader who would like to go further in these approaches and know the developments for wheigted and/or directed graphs the following book is recommended: Fornito, Zalesky & Bullmore of 2016 named “Fundamentals of Brain Network Analysis”.

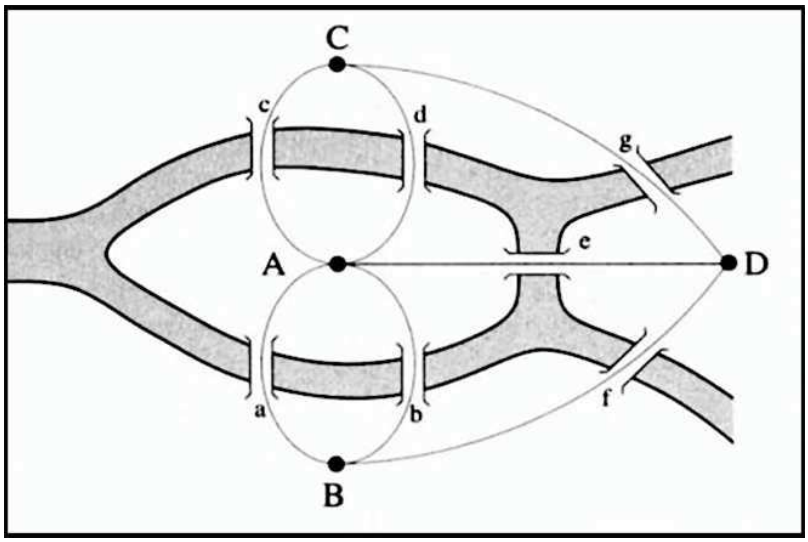

Figure 5F: The problem of the seven bridges of the city of Königsberg and the resolution of the problem of Leonardo Euler.
(From: https://math.stackexchange.com/questions/1173328/eulers-solution-of-seven-bridges-of-königsberg-in-layman-terms)

As we have seen in the previous example of the problem of the seven bridges, the theory of the graphs, not taking into account some variables including location, will therefore require a higher level of extrapolation when the meaning of the results obtained (Fallani et al., 2014). First, we can distinguish two major sub-categories of analytical methods. On the one hand, rather “local” measures that provide information on segregation and, on the other hand, measures that are more of a “diffusion” that will inform the integration of the network (Rubinov & Sporns, 2010). Of course, as we will see in this box, it will be possible to couple these two approaches to characterize as finely as possible the properties of the studied system.

The most affordable and commonly used measure in the literature is the Degree. The degree reflects for each node the number of connections it has with the rest of the graph. The maximum value will therefore depend on the number of nodes included in the analysis. Nodes with a high degree are generally considered Hubs (more connections would imply a larger role in information transfer). Van Den Heuvel & Sporns (2013) have highlighted the essential role of these hubs in particular in the realization of cognitive functions but also the implication of a decrease in their connections in certain pathologies such as Schizophrenia or Alzheimer disease. Nevertheless, some limits can be advanced here (Zalesky et al., 2010) when characterizing a node (for example the size and location of the voxel analyzed in fMRI) or when connected to other nodes (connections between hubs or between smaller nodes).

The two basic measures complementary to the Degree to reflect segregation and intergration are called the Clustering Coefficient and the Pathlength (Figure 5G). The first (Clustering coefficient) reflects the number of triangles formed around an individual node (Watts & Strogatz, 1998). The more triangles there are, the greater the segregation of the network will be (the local connections will be numerous). The Pathlength refers to the path or number of connections that "information" (while remaining very cautious as to the meaning of this term) will have to borrow to link a node A to a node B. The average of all the path of graph denominates the characteristic path length and reflects the global integration of the network.

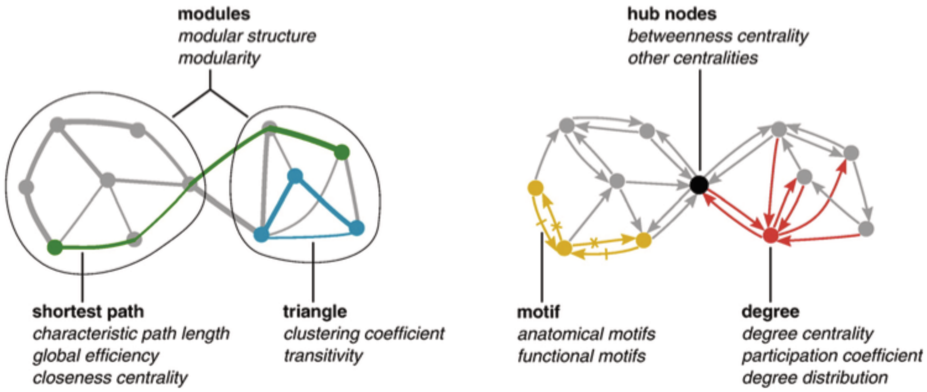

Figure 5G: Example of graph topologies. Degree of a node, Hubs nodes, Clustering coefficiant between three nodes and shortest path between two nodes (From Rubinov & Sporns, 2010).

Finally, one of the oldest formalism and commonly used to quantify both the integration and seggregation which are the two essential properties of the brain in particular (Tononi et al., 1994, 1998) was proposed by Watts & Strogatz in 1998 and is called the small worlds network. These small worlds networks are defined by a topology that is neither totally random nor totally regular, one of the essential properties of the complex systems that we defined at the very beginning of this dissertation in the introduction. These networks are composed of both a high clustering and a low average path length. A regular network will be composed of a high clustering as well as a high path length (conversely for a random network). It is only recently (if we refer to the original works) that these approaches to Graph theory have developed into neuroscience in order to better understand the structural and functional organization of the brain.

Conclusion

The search for a marker of health is a major stake in particular to allow diagnosing the presence of pathologies in the clinical field. Although the first studies using nonlinear approaches proved promising, another side of the literature came to test the functional significance of such approaches. The changes in long-range correlations thought to reflect the complexity of the underlying system were highlighted and would be due to the increased involvement of feedback in performing cognitive-motor tasks. The work carried out in this disseration has allowed us to lay the foundation stone for the possible functional significance of the approach of long-range correlations (mono- and multi-fractals) especially to the work of the concepts of effective adaptation and adaptability. These two entangled concepts are generally used in the literature interchangeably. Nevertheless, our theoretical positioning allowed us to distinguish between these two concepts. Effective adaptation defines as an implementation to perform a task, understood as a capacity already present and possibly exploitable by the system. Adaptability is the ability to achieve this effective adaptation but also the ability of the system to evolve, to discover new solutions that were not present at the beginning. In order to address this fundamental distinction, we have used mono- and multi-fractal analyzes of motor behavior as well as the study of the dynamics of brain networks implemented concomitantly. All our results taken together seem to highlight a different functional meaning of the underlying system between mono- and multi-fractal analyzes, whereas the literature generally considers that this second is only a more precise method of analysis than the first one. From a more systemic point of view, our results highlight a link between the fluctuations of long-range correlations investigated by the multi-fractal analyzes and the number of networks involved at the cerebral level to realize the task under different experimental conditions. This approach linking brain and behavior constitutes a step forward with respect to previous literature, showing a relationship between the systems organization and its output variability across observation levels. It is promising since the number of networks involved would also reflect the effective adaptation made by the subject and therefore possibly a potential marker to diagnose the loss of the adaptation of a subject. Finally this approach comes to question when the possible use of tools such as transcranial electrical stimulation generally used continuously and at a fixed brain site, which would not increase the dynamic of the number of available networks. Of course, other complementary studies are necessary, notably using learning or recovery paradigms after pathology to distinguish more clearly the functional significance of these long-range correlations and their possible clinical diagnostic potential.

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Résumé de la thèse en français

Adaptabilité et adaptation dans une tâche sensorimotrice : de la signification fonctionnelle des propriétés fractales à la dynamique des réseaux cérébraux

Introduction

L'un des objectifs majeurs en neurosciences est de tenter de trouver des marqueurs de santé permettant d'aider à la détection de pathologies. Cette tâche demeure néanmoins ardue étant donnée la composition de l'être humain que ce soit à la fois par les éléments le constituant, mais également par les multiples interrelations que ces éléments entretiennent entre eux. L'être humain peut être considéré comme le système complexe par excellence. L'étude de ces « systèmes » implique l'emploi d'outils et de manières de pensées spécifiques. Dans ces approches, le système est considéré comme un tout. Les éléments constituant ce système ne peuvent être appréhendés de façon indépendante au risque de rester réducteur. Cela implique dès lors la prise en compte des liens entre les éléments. Les systèmes complexes sont considérés comme possédant une organisation fonctionnelle optimale entre deux extrêmes : l'ordre et le désordre (ou entre le cristal et la fumée, selon Henry Atlan). Cette position oscillant entre deux extrêmes implique de fait une possible dynamique temporelle et/ou spatiale de ces systèmes avec des périodes tendant parfois vers plus d'ordre et parfois vers plus de désordre. La complexité définie précédemment doit nécessairement se distinguer du sens communément utilisé au quotidien, où la complexité fait généralement référence à la complication, comme agrégation massive d'éléments ou de liens par exemple.

Dans le champ pluridisciplinaire des sciences du mouvement humain, cette approche dite systèmes complexes a fait l'objet d'un intérêt croissant depuis plusieurs années. L'étude de la dynamique des systèmes notamment au travers de variables macroscopiques comportementales a permis de mettre en évidence certaines propriétés fonctionnelles essentielles n'étant pas prises en compte par le passé. En ce sens, de nombreux auteurs ont étudié ces systèmes complexes à l'aide de l'analyse des séries temporelles produites lors de tâches expérimentales cognitivo-motrices. Alors que les fluctuations, notamment de performance dans la réalisation répétée d'une tâche, sont généralement considérées comme

suivant une distribution gaussienne et sans dépendance entre elles, l'analyse des séries temporelles employant de nouveaux outils mathématiques a mis en évidence d'autres propriétés statistiques complémentaires. Des fluctuations du rythme cardiaque à celles entre les pas dans des tâches de marche, en passant par l'auto-évaluation quotidienne de l'estime de soi, de nombreux auteurs ont souligné la présence de corrélations dites « à long terme » (CLT) entre les données successives étudiées. Ces corrélations à long terme sont également appelées dans la littérature bruit rose ou bruit 1/*f*. Ces CLT impliquent que la valeur actuelle dépend au moins en partie de plusieurs valeurs précédentes produites. Si la série temporelle présente une tendance à l'accroissement, elle aura une plus grande probabilité statistique de suivre cette tendance. Dans le présent travail, ce type de bruit 1/*f* est à distinguer du bruit blanc qui se compose de données n'ayant pas de dépendances statistiques entre elles. L'autosimilarité statistique est une seconde essentielle mise en évidence dans ce type de séries temporelles. Cela signifie que quelle que soit l'échelle d'observation, que ce soit sur l'année, le mois, le jour ou l'heure, la série temporelle observée aura les mêmes propriétés que celles observées à d'autres échelles de temps. Cette autosimilarité est d'importance notamment dans la possible découverte de marqueurs cliniques qui doivent généralement être rapides à extraire. Ces deux propriétés étudiées ensemble reflètent les caractéristiques des séries temporelles dites fractales.

À la suite de la découverte de ces propriétés statistiques spécifiques, de nombreux chercheurs se sont attachés à étudier un grand nombre de séries temporelles extraites à de multiples échelles spatiales du comportement et chez de nombreuses populations. Il a dès lors été mis en évidence que ces propriétés fractales tendaient à diminuer ou à disparaitre chez les sujets souffrant d'une pathologie par rapport aux des sujets sains. Par exemple, cela est le cas dans les battements cardiaques de sujets présentant une arythmie, dans les intervalles de pas au cours de la marche chez des sujets atteints des maladies de Huntington, d'Alzheimer ou de Parkinson, ou encore au niveau de la stabilité posturale chez des sujets âgés. Dans ces études, les auteurs considèrent généralement que l'altération de ces propriétés fractales, tendant vers des séries temporelles aléatoires ou à l'inverse trop prédictibles, reflèterait une perte de complexité du système sous-jacent. Du fait du foisonnement de preuves empiriques dans de multiples paradigmes expérimentaux et pathologies, l'étude des séries fractales s'est révélée prometteuse pour trouver un marqueur permettant de discriminer les sujets sains des sujets pathologiques.

Néanmoins, ce potentiel marqueur s'est vu éprouver par des études plus fondamentales menées sur des populations saines dans des paradigmes expérimentaux classiquement réalisés en laboratoire. Les auteurs de ces études ont en effet mis en évidence qu'une altération similaire de ces propriétés fractales pouvait être observée en fonction des conditions expérimentales imposées aux sujets, en dehors de tout contexte pathologique. Par exemple, dans des tâches telles que le pédalage sur ergocycle, l'ajout d'un feedback visuel pour contrôler la vitesse par rapport à une condition sans feedback entraîne un blanchiment des séries temporelles produites. De nombreux résultats comparables ont été observés comme dans la production de force, dans des tâches de pointage et de Fitt's ou encore lors de coordinations bi-manuelles. Ces études mettent ainsi en évidence que l'ajout de feedback pour réaliser une tâche entraîne une altération des propriétés fractales dans les séries produites. L'explication avancée est que les séries fractales sont produites par des systèmes complexes évoluant de manière naturelle et que l'ajout de feedback entrainerait une contrainte imposée au système.

À la vue des deux approches présentées ci-dessus, il semble y avoir un possible facteur confondant dans l'explication causale de l'altération des propriétés fractales dans les séries temporelles produites. Cela remet donc en question leur capacité à refléter une éventuelle diminution ou une perte de complexité du système étudié, ainsi que leur réel pouvoir diagnostique dans le contexte de différentes pathologies. Une explication plausible serait que face à l'avancée en âge ou au développement d'une pathologie, les sujets mettraient en place des mécanismes de régulation accrus pour réussir à réaliser la tâche. Dans une tâche de marche par exemple, une personne âgée utiliserait / prendrait plus en compte les informations sensorielles internes et externes disponibles pour maintenir son équilibre et sa vitesse de marche. L'utilisation accrue de ces ressources entrainerait une contrainte de fonctionnement comme le reflètent les travaux étudiant la diminution de la fractalité avec l'ajout de feedback. Cette hypothèse supposerait donc que les séries temporelles présentant des propriétés fractales refléteraient l'adaptation effectivement réalisée par le sujet pour réaliser la tâche demandé (en fonction des contraintes) et non pas la complexité ou perte de complexité du système (sujet) directement. Tenter de mieux comprendre la signification fonctionnelle des propriétés fractales permettrait donc de renforcer l'idée selon laquelle ces méthodes puissent se révéler de potentiels bio-marqueurs de santé ou si celles-ci reflètent l'adaptation effective du sujet pour réaliser la condition expérimentale imposée par le chercheur.

Nous pouvons ainsi distinguer d'un point de vue plus théorique le lien entre la complexité du système et sa capacité à s'adapter. Nous avons précédemment utilisé le terme d'adaptation effective. Ce terme peut se référer à la notion de robustesse du système. Bien que celui-ci puisse subir des perturbations internes et / ou externes, la capacité fonctionnelle (ex. produire un mouvement avec un niveau de performance) restera identique. Nous pouvons voir cela comme un réservoir de possibilités déjà acquises par le passé. Dans le présent travail, la distinction est explicitement faite avec l'adaptation au sens évolutionniste qui sera mise en œuvre, par exemple, lors des situations d'apprentissage. Enfin, la notion d'adaptabilité bien que partiellement dépendante des deux propriétés présentées par les systèmes complexes définis ci-dessus peut être définie comme étant à la fois la capacité de robustesse du système et sa capacité à évoluer.

Les notions de robustesse et de capacité à l'évolution se retrouvent dans la littérature comme étant deux propriétés essentielles des systèmes complexes possiblement liées par le concept de dégénérescence (au sens physique du terme). Contrairement à l'utilisation de ce terme au sens commun qui se réfère par exemple à l'évolution progressive d'une pathologie, la littérature en physique ou en biologie définit ce concept comme une relation « plusieurs pour un ». Selon ces auteurs, différentes configurations structurelles pourraient réaliser la même fonction. Cela impliquerait donc que la capacité de robustesse du système se reflète dans le nombre de structures présentes dans le système. L'atteinte ou la disparition d'une seule structure n'impliquerait pas de modification de la fonction puisque d'autres pourraient en prendre la suite. Il y aurait dès lors un nombre minimum de structures requises pour conférer la robustesse à un système. Concernant l'évolution, la dégénérescence se verrait comme étant la capacité du système à créer de nouvelles structures qui n'étaient pas existantes par le passé. Ce concept de dégénérescence fait directement écho au phénomène d'intermittence. Si plusieurs structures peuvent réaliser la même fonction, lors de la réalisation d'essais successifs d'une tâche ou lors d'une tâche continue, différentes structures pourraient se relayer pour maintenir le niveau de performance exigé.

Au niveau du cerveau humain, la littérature a mis en évidence que celui-ci possédait une organisation comprise entre intégration et ségrégation. L'intégration fait référence à l'organisation collective de plusieurs parties le constituant pour réaliser une fonction alors que la ségrégation, quant à elle, se reflète au travers de zones spécialisées qui auront une fonction spécifique dans la réalisation d'une tâche. L'intégration et la ségrégation peuvent dès lors se

voir comme un processus dynamique impliqué de manière plus ou moins intermittente pour la réalisation d'une fonction. En ce sens, étudier le phénomène d'intermittence des réseaux cérébraux pourrait refléter les capacités de dégénérescence au niveau cérébral.

Par conséquent, les études expérimentales présentées dans le cadre de cette thèse visent à distinguer, dans un premier temps, les capacités d'adaptation effectives du système de son adaptabilité en étudiant les propriétés fractales des sujets et, dans un second temps, à tenter de relier ces propriétés fractales au niveau du comportement à la dynamique des réseaux cérébraux. Notre première étude avait pour ambition de dé-corréler au niveau de la production motrice la signification fonctionnelle des propriétés mono- et multi-fractales en terme d'adaptation effective et d'adaptabilité. La seconde étude visait à comprendre le lien possible entre ces propriétés fractales du comportement en lien avec la dynamique des réseaux cérébraux. Enfin, notre dernière étude avait pour objectif de proposer un nouvel apport méthodologique dans l'investigation des liens dynamiques entre les aires cérébrales.

Contributions personnelles

Étude 1 : *Adaptabilité ou adaptation : Signification fonctionnelle des propriétés fractales.*

La présence de propriétés fractales dans les séries temporelles a été mise en évidence dans la littérature par un grand nombre d'études investiguant, d'une part, des conditions expérimentales avec contraintes changeantes et, d'autre part, l'effet de différentes pathologies. Les hypothèses présentées dans ces deux types d'approches sont potentiellement contradictoires. Pour l'une, l'implication accrue de feedback imposerait une contrainte au système, entraînant une altération des propriétés fractales. Pour l'autre, la perte ou diminution de fractalité des séries temporelles serait liée à une perte de complexité du système sous-jacent, notamment due à la pathologie ou l'avancée en âge. Le but de cette première étude était donc de mieux comprendre la signification fonctionnelle des propriétés fractales. Notre hypothèse était la suivante : les propriétés mono-fractales refléteraient l'adaptabilité du système tandis que les propriétés multi-fractales refléteraient, quant à elles, l'adaptation effective mise en œuvre par un système fonctionnant sous contrainte.

Quatre-vingt-quatorze sujets sains ainsi qu'un patient désafférenté ont pris part à cette étude. Ces sujets ont été répartis en 8 groupes expérimentaux imbriqués : un groupe contrôle, un

groupe avec suppression d'un feedback (visuel ou auditif ou proprioceptif), un groupe avec suppression de deux feedback (visuel et/ou auditif et/ou proprioceptif), un groupe avec suppression de trois feedbacks (visuel, auditif et proprioceptif). La tâche motrice consistait en un paradigme de tape de l'index en synchronisation-continuation avec un métronome d'une durée de six minutes et quarante secondes (chaque sujet réalisant trois essais). Les intervalles inter-tapes ont été extraits puis analysés grâce aux variables suivantes : la moyenne, le coefficient de variation, la dérive, la *Detrended Fluctuation Analysis* (DFA ; mono-fractale) et la *Multifractale Detrended Fluctuation Analysis* (MF-DFA ; multi-fractale). Les analyses restent à ce jour préliminaires dans le sens où seules les conditions sans la suppression de la proprioception ont été analysées ainsi que le participant désafférenté.

Nos résultats n'ont pas montré de différences significatives entre les conditions contrôle, moins un et moins deux feedback pour les variables de performance que sont la moyenne, le coefficient de variation et la dérive. En revanche, le participant désafférenté présentait une différence significative avec le groupe moins deux feedback pour la moyenne ($p < 0,001$), le coefficient de variation ($p < 0,001$) et la dérive ($p < 0,01$). Concernant l'analyse mono-fractale, aucune différence significative n'a été montrée concernant nos groupes expérimentaux. Néanmoins, le patient désafférenté était statistiquement différent du groupe moins deux feedback ($p < 0,001$). Enfin, concernant l'analyse multifractale, une différence significative a été observée entre le groupe contrôle et le groupe moins deux feedback ($p = 0,03$) ainsi qu'en le groupe moins deux feedback et le patient désafférenté ($p < 0,001$).

En conclusion, ces résultats préliminaires considérés conjointement mettent en évidence une diminution de la performance et une modification des propriétés fractales dans les séries temporelles chez le sujet désafférenté. De plus, les propriétés mono- et multi-fractales évoluent différemment. L'augmentation des propriétés multi-fractales de manière conjointe aux nombres de feedback supprimés pourrait refléter l'adaptation effective mise en œuvre pour réaliser la tâche. Les analyses mono-fractales, quant à elles, pourraient refléter l'adaptabilité du système.

Étude 2 : *Changements conjoints de la connectivité fonctionnelle cérébrale et de la variabilité motrice pour s'adapter aux contraintes de la tâche.*

D'un point de vue théorique le cerveau peut être perçu comme étant dans une balance dynamique entre intégration et ségrégation fonctionnelle. À une échelle d'observation donnée, le cerveau s'organise de manière modulaire, ce qui signifie que certaines parties sont densément connectées à l'intérieur d'elles, mais faiblement connectées entre elles. De plus, la complexité au niveau cérébral se reflète à travers ces propriétés dynamiques qui, peuvent en fonction des contraintes internes ou externes imposées au système, se reconfigurer pour réaliser une fonction. Ces propriétés font référence à la dégénérescence de son organisation structurelle impliquée de manière plus ou moins intermittente. Ces capacités confèrent au système une robustesse d'évolution qui prises ensemble reflètent l'adaptabilité du système. Au niveau du contrôle moteur, cette dégénérescence du système se refléterait au travers des analyses multi-fractales. Un plus grand nombre de structures impliquées entraînerait une augmentation des propriétés multi-fractales au niveau comportemental. À la vue de notre première étude et de la littérature portant sur la dynamique des réseaux cérébraux, nous avons émis l'hypothèse selon laquelle l'augmentation du niveau de multi-fractalité devait co-varier avec le nombre de réseaux cérébraux mis en œuvre de manière conjointe pour réaliser la tâche.

Trente-deux sujets ont pris part à cette étude. Ces derniers ont été répartis en quatre groupes expérimentaux comme suit : contrôle, moins un feedback (réalisant chacun une condition de suppression du feedback visuel, auditif, tactile de manière randomisée), moins deux feedback (visuel et auditif, auditif et tactile, tactile et visuel) et moins trois feedback (visuel, auditif et tactile). Nous avons utilisé le même paradigme expérimental que dans l'étude précédente, chaque sujet réalisant une tâche de tape de l'index en synchronisation-continuation de six minutes et quarante secondes. Les variables au niveau comportemental (performance) étaient la moyenne, le coefficient de variation et la dérive des intervalles inter-tapes. Les propriétés fractales étaient analysées grâce à la DFA et la MF-DFA. Les réseaux cérébraux ont été étudiés grâce à une méthode de neuro-imagerie non invasive, la spectroscopie dans le proche infrarouge (fNIRS). Après avoir extrait la connectivité fonctionnelle par fenêtre glissante entre les canaux fNIRS couvrant les régions sensori-motrices, nous avons opté pour une analyse de détection de communautés permettant d'extraire notre variable d'intérêt qui était le nombre de réseaux différents mis en œuvre au cours de la tâche.

Nos résultats n'ont pas mis en évidence de différence significative entre les quatre groupes expérimentaux concernant les variables de performance (moyenne, coefficient de variation et dérive). Il en était de même pour l'analyse mono-fractale. L'analyse multi-fractale (MF-DFA) a mis en évidence une différence significative de performance entre le groupe contrôle et les groupes moins un et moins deux feedback ($p = 0,012$ et $p = 0,021$, respectivement). Concernant notre variable au niveau cérébral de nombre de réseaux mis en œuvre, les analyses ont révélé une différence significative entre le groupe contrôle et les trois autres groupes expérimentaux ($p = 0,003$). Enfin nous avons mis en évidence une corrélation positive significative entre la variable multi-fractale et le nombre de réseaux mis en œuvre ($p = 0,028$).

En conclusion, ces résultats permettent de mettre en avant une évolution conjointe de la multi-fractalité au niveau du comportement ainsi que du nombre de réseaux sans que cela n'entraine de diminution de performance au niveau comportemental. Cela appuie un peu plus l'idée selon laquelle les analyses multi-fractales refléteraient les adaptations effectives mises en œuvre par les sujets pour réaliser la tâche en fonction du nombre de feedback dont les sujets ont été privés. De plus, à l'instar de la première étude, les propriétés mono-fractales refléteraient l'adaptabilité des personnes face aux contraintes externes.

Étude 3 : *La dynamique des réseaux du cerveau humain révélée par l'analyse temps/fréquence de la connectivité effective en SPIR.*

La dynamique des réseaux cérébraux est maintenant reconnue comme étant une propriété essentielle à la robustesse et la capacité à s'adapter de l'être humain. Néanmoins, les premières approches utilisées dans notre étude précédente peuvent être complétées par d'autres méthodes d'analyse. L'utilisation d'un coefficient de corrélation (par exemple de Pearson) en fenêtre glissante va entraîner en premier lieu un choix a priori de l'expérimentateur concernant la taille de fenêtre à prendre en compte. De plus, cette méthode bi-variée semble dès lors limitée avec le nombre croissant de séries temporelles collectées de manière simultanée pouvant entrainer un phénomène de transitivité. Enfin celle-ci ne permet pas de mettre en évidence la directionalité du lien pouvant s'exercer en deux aires cérébrales distinctes.Dans cette troisième partie, notre hypothèse était la suivante : des analyses plus

« poussées » pourraient refléter l'influence qu'une région cérébrale exercerait sur une autre dans une tâche sensorimotrice prolongée.

Six sujets extraits du groupe contrôle de notre seconde étude ont été étudiés. Le paradigme expérimental consistait, comme précédemment, à une tâche de tape de l'index en synchronisation-continuation sans suppression de feedback. Les données ont été collectées via fNIRS. Après avoir réalisé un prétraitement des données pour limiter la présence d'artefacts, nous avons appliqué une méthode d'analyse récente appelée *Time-Resolved Partial Directed Coherence* (tPDC). Utilisant un double filtre Kalman étendu, cette méthode permet d'extraire un modèle autorégressif multi-varié à chaque instant et pour chaque bande de fréquences constituant le signal fNIRS. Ensuite, une analyse de cohérence partielle dirigée a été appliquée à chacun de ces modèles autorégressifs. Les variables d'intérêt pour ces séries temporelles étaient ensuite extraites (moyenne, écart-type et entropie).

Les séries « brutes » extraites de l'analyse ont fait l'objet d'un test de surrogate. À la suite de cette première analyse, dix-huit connections sur trois cent six se sont montrées statistiquement différentes par rapport à des séries aléatoirement générées. Concernant la moyenne, le cortex pré-moteur droit (CPMd) vers le gauche (CPMg) était statistiquement différent des cortex pré-frontaux dorsolatéraux bilatéraux et orbito-frontaux bilatéraux ($p < 0,05$). Les connexions entre le cortex moteur gauche (CMg) vers le CPMg et du cortex moteur droit (CMd) vers le CMg étaient statistiquement différentes des connections bidirectionnelles pour le cortex préfrontal ($p < 0,05$). Concernant l'écart type et l'entropie, les résultats étaient identiques aux précédents avec de plus : une différence significative entre CMg vers CMd comparée aux connexions préfrontales et CMd vers CMg comparée à la connexion orbito-frontale gauche vers orbito-frontale droite.

Ces résultats d'ensemble mettent en évidence 18 connexions qui sont en concordance avec la littérature utilisant d'autres méthodes de neuro-imagerie investiguant la réalisation d'une tâche sensorimotrice uni-manuelle simple. L'utilisation d'analyses multi-variées combinées à des surrogates permet de limiter les connexions fallacieuses et les phénomènes de transitivité rencontrés par les analyses couramment utilisées dans la littérature. Par ailleurs, la mise en évidence de connexions unidirectionnelles permet d'ouvrir de nouvelles pistes d'investigation en utilisant la fNIRS.

Discussion générale

L'étude des systèmes complexes via l'analyse en série, et plus particulièrement la caractérisation des propriétés fractales, s'est révélée prometteuse depuis environ deux décennies. Néanmoins, ces études restent généralement cloisonnées à l'étude d'une série temporelle extraite à un seul niveau d'investigation (comportemental, cérébral, cardiovasculaire, etc.). Avec la mise en évidence d'une diminution de la présence de ces propriétés fractales, ces approches sont éprouvées notamment dans la quête de la découverte d'un marqueur de santé général et fiable. Il est dès lors nécessaire de croiser ces approches théoriques et d'étudier de manière conjointe différents niveaux d'observations pour tenter de mieux comprendre la signification fonctionnelle de ces propriétés fractales présentes dans les séries temporelles produites par l'organisme.

Dans un premier temps, nos études ont mis en évidence que les analyses mono- et multi-fractales n'évoluent pas de manière conjointe. Alors que la performance restait inchangée bien que les sujets étaient perturbés par des différentes suppressions de feedback, les analyses multi-fractales ont mis en évidence une évolution entre le groupe contrôle et les autres conditions. L'augmentation du degré de multi-fractalité permet, dans un premier temps de faire l'hypothèse que cette analyse reflète l'adaptation effective du sujet pour réaliser la tâche. Moins le sujet dispose de feedback, plus celui-ci va explorer différents sous-systèmes pour maintenir un niveau de performance identique à celui des sujets contrôles. Ce résultat semble se confirmer dans notre deuxième étude avec une augmentation du nombre de réseaux cérébraux mis en jeu au cours de la tâche. D'autre part, les analyses mono-fractales ne montrent pas de différence significative entre les conditions expérimentales dans les deux premières études. Seul le patient désafférenté présente une diminution des propriétés mono-fractales dans les séries temporelles produites.

Dans un second temps, les analyses multi-fractales ont mis en évidence une différence entre le groupe contrôle dans notre seconde étude et les groupes ayant réalisé la tâche avec moins un, deux, ou trois feedback. Corrélés avec le nombre de réseaux cérébraux obtenus dans notre seconde étude, ces résultats suggèrent que, sous contraintes, le système va exploiter de manière transitoire différents sous-systèmes pour continuer à réaliser la tâche à un même niveau de performance. L'exploitation transitoire de ces sous-systèmes serait le reflet de la dégénérescence du système, lui permettant ainsi une certaine robustesse bien que les

contraintes soient différentes pour réaliser la tâche. Néanmoins, notre patient désafférenté produit des séries temporelles avec un degré de multifractalité plus important que les autres groupes expérimentaux. Si ces analyses reflètent l'adaptation effective des sujets, nous pouvons faire l'hypothèse de l'existence d'un degré de multifractalité maximum au-delà duquel le système ne serait plus capable de s'adapter et entraînerait dès lors une diminution de la performance. Pour répondre à cette hypothèse, il nous faudrait pouvoir augmenter les contraintes de manière progressive jusqu'à atteindre le point où la performance ne peut plus être maintenue. Des études de simulation ou le recours à des modèles animaux pourraient nous aider dans ce sens. Pour nous permettre de distinguer la signification fonctionnelle des propriétés fractales, notamment en termes d'adaptation effective, d'adaptation en termes d'évolution et d'adaptabilité, il nous faudrait poursuivre nos travaux entre autres dans des processus d'apprentissage, ce qui nous permettrait de tester dans un même paradigme la robustesse du comportement ainsi que ses capacités à évoluer.

Enfin, notre troisième étude nous a permis de proposer une nouvelle méthode d'analyse qui refléte la directionnalité des liens entre régions cérébrales et leurs dynamiques. Nous avons ainsi mis en évidence des fluctuations différentes dans le réseau sensorimoteur impliqué dans la réalisation de la tâche. Appliquer cette méthode aux données extraites des quatre conditions expérimentales utilisées dans notre seconde étude permettrait de mieux comprendre l'intermittence de fonctionnement des réseaux et leur possible lien avec le niveau de multifractalité au niveau du comportement.