Function of the Human Cerebellum in Timing and Auditory-Motor Synchronisation

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I hereby declare that this dissertation is my own work, except as indicated in the text.
Signature:
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Abstract

This thesis is divided into two main parts: introduction and experimental research. **Chapter 1** and **Chapter 2** in the introduction provide a theoretical background for the experimental research presented in **Chapters 4–6**. **Chapter 3** includes a description of the general methods, set-up and measures used in the experimental research.

Chapter 1 opens with some general considerations on the concept of time in cognitive psychology, followed by a classification of timing abilities. Timing processing is conceptualized as the ability of the brain to track the passage of time and to process temporal properties of exogenous sensory stimuli. Timing ability is thought to be fundamental to both perception and action. After a general introduction on timing, the topic moves onto auditory-motor synchronisation, a behaviour that is thought to rely on temporal processing. This section includes an account of auditory-motor synchronization both in human and in other species, and a discussion of the clinical relevance of auditory-motor synchronization.

Chapter 2 is dedicated to the cerebellum, a structure at the back of the brain that is the focus of the work presented in this thesis. The chapter includes a description of cerebellar anatomy, function and dysfunction.

The second part of the thesis opens with a general method section, **Chapter 3**, which includes a concise description of techniques, methods and measures used in the experimental research, as well as some descriptions for standard practices.

Following on, **Chapter 4** is a report of two behavioural experiments on perceptual timing (Zeni & Holmes, 2018). The aim of these experiments was to examine whether a regular sequence of sounds can modulate the perceived duration of time intervals embedded in the sequence, as shown by Barnes and Jones (2000). These experiments should have provided the grounding for the following research on motor timing, but the result did not replicate. An argument was made around the impact of methodological choices on the results.

Chapter 5 is a report of two cerebellar transcranial magnetic stimulation (TMS) experiments that were run to examine whether single-pulse TMS delivered over the

cerebellum could be used to interfere with auditory-motor synchronization, studied with the finger-tapping task. Notice that a similar use of repetitive TMS had been proven successful. Both intermittent and continuous rhythmic movements were examined, to test the hypothesis of dissociation between these two movement types, as suggested by previous behavioural and clinical evidence. TMS affected finger-tapping performance, but the effect observed, which was short-lasting and not hemispheric-specific, most likely resulted from the discomfort and the non-habituating startle-like reflex elicited by TMS, rather than from a direct interference of the stimulation with cerebellar function.

Chapter 6 is a report of a two-session, simultaneous EMG-fMRI experiment on the function of the cerebellum in auditory-motor synchronization. In this experiment, both intermittent and continuous rhythmic movements, both paced and unpaced by an external auditory stimulus, were examined. Intermittent and continuous rhythmic movements are thought to require different processing, and the cerebellum is suggested to be involved in this dissociation. More specifically, temporally constrained intermittent movements are thought to rely on cerebellar functioning. Representational similarity analysis was used to test whether the difference between intermittent and continuous movements and between paced and unpaced tasks were encoded in the functional activity of the cerebellum. Alternative models built out of behavioural data were tested to decide whether the cerebellum was more likely to encode aspects specific to synchronisation performance, rather than motor execution. Contrary to predictions, continuous movements activated the cerebellum (ipsilateral lobules V, VI and VIII) more than intermittent movements. Moreover, this activation was more likely to reflect differences in the motor component of the task, rather than aspects of synchronisation performance.

The thesis concludes with a general discussion of the experimental work, reported in **Chapter 7**. This final chapter includes a summary of the research questions addressed, a description of how the conclusions are supported by the results and are integrated in the existing body of knowledge. Limitations and implication for future studies were also discussed.

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I dedicate my PhD to my family.

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Introduction

Chapter 1. Timing and Auditory-Motor Synchronization

1.1 The concept of timing in cognitive psychology

Time pervades our lives and determines the quality of our conscious sensations. This fact may lead us to believe that the construct of time is fundamental to the understanding of brain functioning. In an hypothetical study of the brain, we would posit the existence of a *timing system*, a system of interconnected areas in the brain, apt at processing the temporal properties of both endogenous and exogenous events. We would also adopt the term *timing processes* to refer to the neural activity of this system. As humans, we tend to reason around unfamiliar subjects by analogy to other humans, so we would soon start to refer to this timing system as *the timekeeper*. This terminology has been adopted by researchers within an information processing standpoint and is in current use in the field of cognitive psychology and neuroscience. One might question whether studying how the brain processes time is appropriate at all, since time is an abstract concept and may be considered as a mere epiphenomenon, not less than consciousness, free will, or qualia[1]. Relying on an abstract concept to provide an objective classification of mental processes is problematic: as the philosopher Ludwig Joseph Johann Wittgenstein pointed out in his Tractatus Logico-Philosophicus (1922), abstract words cannot be unequivocally defined, because they do not refer to a particular instance in the outside world, therefore their characteristics cannot be acknowledged once and for all. This ambiguity in meaning can only be resolved by boiling abstractions down to practical examples. On the other hand, avoiding the use of the current terminology would hinder an effective communication of the results. In this thesis the use of all terms related to the concept of time will primarily be used to characterize the behaviour, in reference to tasks, goals and abilities. Analogous terms will occasionally be referred to mental processes, with the aim to explain existing accounts.

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[1] Plural of the Latin "qualis", meaning "of what sort", term used in reference to individual instances of

1.2 Sub-second and supra-second timing

Distinct timing abilities have been associated with distinct neural systems or systems of brain regions that can process temporal information of different orders of magnitudes, with a varying degree of precision. One proposed dissociation distinguishes the abilities to estimate the duration of *sub-second* and *supra-second* intervals (Rubia et al., 1998, Lewis & Miall, 2003). Sub-second timing has been linked to motor control, since movement execution is characterized by high temporal control, in the order of tens or hundreds of milliseconds (Hore et al., 1991). For example, dance, speech and music are all thought to rely on this timing system for good functioning (Buhusi & Meck, 2005). Instead, the supra-second timing is more often linked to learned behaviours such as social interaction or foraging (Brunner et al., 1992; Pyke et al., 1977). The neural basis for sub-second timing has been localized in motor regions of the brain, while the supra-second timing would rely more on prefrontal and parietal regions (Lewis & Miall, 2003). It has also been proposed that the two timing systems differ in the degree of cognitive control: while sub-second processing is thought to be automatic, supra-second processing would require voluntary cognitive control (Buhusi & Meck, 2005; Lewis & Miall, 2003).

1.3 Duration-based and beat-based timing

As a further dissociation relevant to the present work, timing ability has been dissociated into *duration-based* (or *absolute*), and *beat-based* (or *relative*) timing. Duration-based timing is defined as the ability to estimate the duration of single events, while beat-based timing is the ability to estimate the duration of events embedded in a context of other preceding, overlapping and following events, where the context can induce in the listener a perception of beat. Evidence for a dissociation between duration-based and beat-based timing comes from clinical studies: On the one hand, patients with cerebellar ataxia were shown to be impaired at estimating the duration of intervals between sounds, when the intervals were presented in isolation, but not when these same intervals were presented after a sequence of regularly spaced sounds (Teki et al., 2011; Grube et al., 2010). On the other hand, Parkinson's disease (PD) patients were shown to perform worse than healthy controls in tasks that require the discrimination of rhythms with a weak beat, but not in duration-based temporal tasks, like for example temporal discrimination (Artieda et al., 1992; Nichelli et al., 1996; Harrington et al., 1998; Grahn & Brett, 2009). This dissociation between duration-based and beat-based timing is also supported by evidence from neuroimaging studies, which suggest a role of the cerebellum in absolute timing (Petacchi et al., 2005) and of the basal ganglia in relative timing (Grahn & Brett, 2007; Grahn & Rowe, 2009). In the perceptual domain, duration-based timing relies on the olivo-cerebellar network comprising inferior olive, vermis, and deep cerebellar nuclei (Grube et al., 2010; Teki et al., 2011). Beat-based timing recruits the striato-thalamo-cortical network and involves basal ganglia, thalamus, premotor cortex, supplementary motor area (SMA) and dorsolateral prefrontal cortex (DLPFC). Even though the two systems include separate distributed systems of cortical and subcortical areas of the brain, they are anatomically and functionally interconnected and are thought to work as a unified system (Teki, Grube, & Griffiths, 2012).

1.4 Internally-based and externally-cued timing

Perceptual and motor timing can be distinguished also on the basis of whether timing is *internally-based* or *externally-cued*. In internally-based timing a perception or a behaviour, in the absence of an external cue, has to rely on an endogenous representation of time. Examples of tasks that require internally-based timing are: duration discrimination, the ability to estimate and compare the duration of events; interval production, responding to a stimulus after a required amount of time has elapsed; and finger-tapping continuation, tapping at the same pace of a previously cued rhythm. When timing is externally-cued, instead, temporal constraints are provided by an exogenous stimulus. A typical example of externally-cued timing is sensorimotor synchronization, which requires people to move in synchrony with a periodic stimulus (e.g., a sequence of tones or of flashing stimuli) and is typically studied with the finger-tapping task. In finger-tapping synchronization, participants rely on the temporal invariances present in the stimulus to coordinate their action.

An activation likelihood estimation (ALE) meta-analysis on 177 fMRI experiments specifically examined the neural substrates of internally-based and externally-cued timing (Teghil et al., 2019). Timing tasks activate a broad network of areas, including bilateral SMA, intraparietal sulcus (IPS), inferior frontal gyrus (IFG), anterior insular cortex and basal ganglia (BG, in particular the putamen), right posterior superior temporal gyrus (pSTG) and left precentral gyrus (PCG) were also activated. Bilateral activation in SMA, frontal regions and BG were found in both internally-cued and externally-based timing tasks. This result is supported also by previous voxel-wise meta-analyses (Radua et al., 2014; Wiener et al., 2010). However, left SMA, PGC and insula, and a cluster in IFG were activated more by externally-based than internally-cued tasks, while the reverse contrast did not produce any supra-threshold cluster of activation (Teghil et al., 2019). This result suggests that internally-based timing may rely on a subset of areas involved also in externally-cued timing. One thing to notice is that the cerebellum is not part of this network; this may be in part due to the fact the cerebellum is often neglected in fMRI experiments, since the typical acquisition sequence does not contain enough slices to cover the whole brain.

1.5 Musical rhythm

In the auditory domain, the ability to perceive the duration of sounds in the sub-second range, together with the ability to detect temporal regularities in a sequence of auditory events are thought to be fundamental to the practice of dance and to music perception and production, among a number of other cognitive abilites (Buhusi & Meck, 2005). Humans, unlike most other species, show a spontaneous and automatic tendency for auditory-motor synchronization, the tendency to entrain to regular or rhythmic sounds, with head nodding, toe tapping or humming, which finds its higher expression in the practice of dance (Repp, 2005a; Repp, 2012). This tendency to move in synchrony with a musical rhythm has been observed in many cultures and is considered universal (Repp, 2005a; Nettl, 2000). This distinctive synchronization behaviour is most easily triggered by *groove* music, music that has a persistent repeated pattern that can induce in the listener a *sense of beat*. Jazz, funk, R&B, hip-hop, reggae, some forms of rock and electronic music are all examples of groove music. The sense of beat, a propulsive feel of rhythm, induces in the listener an *urge to move* that is often associated with an intimate sense of pleasure and is rewarding for the organism (Repp, 2005a). It is worth noting that a similar behaviour is not displayed when a visual stimulus presents analogous temporal regularities. For example, humans do not tend to tap their toe in response to a bouncing ball (Patel et al., 2005; Repp & Penel, 2004). Given the unique nature of auditory-motor synchronization behaviour, it is interesting to examine how this behaviour is implemented by the brain and how the cerebellum contributes to this ability.

1.6 Auditory-motor synchronization in humans

Auditory-motor synchronization is the coupling of motor responses to periodic perceptual auditory stimuli. This ability is involved in music and dance and has been studied experimentally for almost a century with the finger-tapping task (see Repp, 2005; Repp, 2013 for a review). In finger-tapping, participants are required to tap their finger in synchrony with a regular or periodic sequence of tones, and align the downward or the upward phase of their oscillatory movement with the sounds presented. Since both perceptual stimuli and motor responses develop in time, rhythmic synchronization has often been associated with the ability of the brain to process temporal information. Numerous variants to the finger-tapping task have been proposed. These involve movements with different muscles and joints (i.e., tapping or circle drawing) or with different kinematics (e.g., intermittent or continuous tapping), different modalities for the coupling stimuli (i.e., auditory, visual), different phases between stimulus and response (i.e., in-phase and in anti-phase tapping) and different frequencies of the motor response relative to the stimulus (e.g., 1:1, 1:2, 2:1, 1:3, etc.). A comprehensive account can be found in Repp (2005a; 2013). Measures of finger-tapping performance are the inter tap intervals (ITI), the time between consecutive taps and the negative asynchronies (NA), the temporal mismatch between each tap and sound.

Even though sensorimotor synchronization to a rhythmic auditory stimulus is thought to occur automatically (Repp, 2005a), not all coordination modes are equally stable. Anti-phase tapping, for example, tends to reverse to in-phase tapping, a phenomenon termed *phase transition*, which is likely to occur with tempo changes. Phase relations other than in-phase and anti-phase are even more difficult to maintain (Haken et al., 1985; Kelso et al., 1990). A second characteristic of auditory-motor synchronization is that this behaviour, can take place in a limited range of *tempi* – i.e., the frequencies at which the stimuli are presented (Fraisse, 1982). This last constraint is motoric, since it depends on how quickly the effector can be moved, and perceptual, since a sense of beat can be elicited only by a limited range of tempi. The lower limit for movement durations in a 1:1 finger-tapping task is estimated around 150-200 ms (Keele & Hawkins, 1982). The perceptual lower limit has been studied by manipulating the frequency of the response over the stimulus from 1:1 to 1:2. This perceptual threshold has been estimated to be around 100-120 ms in skilled participants and musicians (Repp, 2003). Interestingly, the variability of asynchronies decreases from 1:1 to 1:2 with in-phase tapping (*subdivision benefit*, Repp, 2003), although this benefit disappears for intervals of 200-250 ms (Semjen et al., 1992). Anti-phase tapping has a higher lower bound than in-phase tapping (300-350 ms in musicians; Repp, 2005b; 2005c). A striking difference has been found also when comparing in-phase tapping with a visual stimulus and an auditory stimulus: synchronization performance with flashing lights dropped at intervals between stimuli shorter than 460 ms (Repp, 2003). The upper perceptual limit, at approximately 1800 ms (Fraisse, 1982, Engström et al., 1996; Mates et al., 1994a&b), has been attributed to the ability to anticipate the tone. Sounds longer than 1800 ms cannot be anticipated and need to be subdivided in order to be accurately reproduced.

A further distinctive feature of auditory-motor synchronization is given by the negative asynchronies (NAs). When people are asked to tap along with a regular beat, finger taps tend to precede tones by a few tens of milliseconds, rather than being symmetrically distributed around zero (Repp, 2005a). N*egative* is therefore a synonym for anticipatory. However, It is interesting to note that motor responses do not have to be negative to be anticipatory, as any response that precedes a reaction time to a stimulus (≈ 150 ms) is already based on a prediction (Mates et al., 1994c). Even though NAs are not fully understood, the evidence available suggests that they are likely to depend on the perceived synchrony between the implementation of a motor response and the auditory, visual or tactile feedback that is used by the brain to make this response contingent to the tone. In accordance with this explanation, NAs were found to decrease when additional auditory feedback overlapping with finger taps was provided (Aschersleben & Prinz, 1995; 1997) and to increase when the tactile feedback was reduced with anaesthesia (Aschersleben et al., 2001). Furthermore, NAs can be manipulated by delaying the auditory feedback (Aschersleben & Prinz, 1997). An interesting fact is that reduced NAs were observed in musicians compared to non-musicians (Aschersleben, 2002) and in professional drummers, compared to professional pianists or singers (Fujii et al., 2011).

1.7 Auditory-motor synchronization in other species

Humans are not the only species that can spontaneously synchronize their body movements with an auditory rhythm. Both male and female parrots show spontaneous rhythmic synchronization to a music beat and move in anticipation to the sounds (Patel et al., 2009; Schachner et al., 2009). Renowned is the case of a male sulphur-crested cockatoo called Snowball (**Figure 1.1**).

Figure 1.1 *Snowball, a male sulphur-crested cockatoo (Cacatua galerita eleonora). Figure taken from Patel et al., 2009.*

Snowball showed spontaneous head bobbing and foot lifting to the beat of rhythmic music with tempi ranging from 108 to 132 bpm (Patel et al., 2009; Schachner et al., 2009). Snowball's spontaneous tendency towards synchronization, however, was observed primarily during the presentation of well-known songs and was less evident when new excerpts were played. As it has later been pointed out (Schachner, 2010), human encouragement is likely to have boosted Snowball's dancing behaviour. Surprisingly, after a systematic search and analysis of videos taken from the large database provided by the YouTube website, Schachner and colleagues found extensive evidence of entrainment in animals capable of vocal mimicry, including 14 species of parrots and one elephant, but no evidence in many closely related species incapable of vocal mimicry, including domesticated animals (i.e., cats and dogs), even though these last were over-represented (Schachner et al., 2009; Schachner, 2010). Subsequently, other studies have found evidence of rhythmic entrainment in vocal learners (Patel et al., 2009; Hasegawa et al., 2011). Given that vocal learning, like rhythmic entrainment, involves the coupling between an auditory stimulus and a motor response, it has been hypothesized that rhythmic entrainment is a by-product of vocal learning and should be found only in vocal learning species, such as humans, some birds, cetaceans and pinnipeds (Patel, 2006; Patel et al., 2009).

In accordance with this prediction, spontaneous sensorimotor synchronization was not observed in human primates: even after extensive training, Rhesus monkeys (*Macaca mulatta*) were tapping approximately 250 ms after the sounds, rather than before or aligned with them (Zarco et al., 2009). The fact that response times were shorter for regular than randomly spaced auditory stimuli, however, is evidence for some degree of anticipation. In a later study, phase asynchronies were lowered to 100 ms by adopting a stricter rewarding method (Merchant & Honing, 2014). Despite the fact that Rhesus monkeys can produce tempo-matched sequences of movements for a range of intervals from 450 to 1000 ms (Zarco et al., 2009), they do not tap in anticipation to the sounds as humans do (Repp, 2005a). These studies suggest that the connectivity between the motor and the auditory system might differ between monkeys and humans, and that auditory information might not be available to the motor system of monkeys, as it is in humans (Merchant & Honing, 2014).

Contrary to the hypothesis of vocal learning, evidence for rhythmic entrainment was not found in vocal mimicking species such as songbirds, bats and dolphins (Schachner, 2010), and even though the absence of videos does not provide proof of the absence of rhythmic capacity in these species, it has been suggested that vocal learning might be necessary, but not sufficient to observe rhythmic entrainment. The vocal mimicry hypothesis of rhythmic entrainment, however, is questioned by one study reporting rhythmic entrainment in the sea lion, a non-vocal learner (Cook et al., 2013). In order to reach a consensus, empirical studies of rhythmic abilities in non-human animals are necessary.

To conclude, the study of auditory-motor synchronisation across animal species and cognitive domains is important, because it can help us refine hypotheses on the evolutionary origin of this spontaneous behaviour. Moreover, a hypothesis for a common origin of rhythmic synchronisation can help us identify the neural systems that support its implementation.

1.8 Clinical relevance of auditory-motor synchronization

The pioneering studies of Paltsev and Elner, Rossignol and Melville Jones have shown that loud sounds can raise the excitability of spinal motor neurons measured with the H-reflex (or Hoffmann's reflex) via the reticulo-spinal pathway (Paltsev & Elner, 1976; Rossignol & Jones, 1976); a result that has later been replicated (Rudell & Eberle, 1985; Nakashima et al., 1994; Delwaide & Schepens, 1995). Furthermore, auditory stimulation can increase motor cortex excitability: a loud sound preceding TMS over M1 by 30–50 ms has been shown to suppress MEPs (Furubayashi et al. 2000), while a loud sound preceding TMS by 200 ms has been shown to increase MEPs (Löfberg et al., 2018). Based on this evidence it has been posited that a direct connection between the auditory cortex and the motor system, whether cortical or sub-cortical, enables auditory rhythms to entrain motor behaviour. Numerous clinical studies on the effect of rhythmic auditory stimulation on movements have followed since then, gathering compelling evidence on the beneficial effect of rhythmic auditory stimuli on motor coordination, both in healthy individuals and in patients with motor disabilities (see Thaut et al., 1999 for a review). Rhythmic auditory stimulation (RAS), the presentation of auditory stimuli that induce in the listener a sense of beat, has been shown to improve motor coordination in locomotion: increased stride symmetry, step cadence and stride length were observed when studying gait in PD (Thaut et al., 1996): when Parkinson's patients walked to rhythmic sounds, shape variability in EMG activation measured from the leg muscles tibialis anterior and medial gastrocnemius (MG) was reduced, while bilateral symmetry of EMG gait-cycle profile measured from TA was increased compared to that in healthy elderly participants. These results were considered evidence for more consistent motor unit recruitment (Miller et al., 1996; Hurt et al., 1998). Interestingly, velocity and acceleration profiles of the moving limbs, measured with motion trackers, also became smoother when a rhythmic cue was played. In stroke patients, step cadence and coordination of the paretic and the non-paretic limbs improved when walking to a metronome compared to when walking on a treadmill of varying speed (Roerdink et al., 2007). Similar benefits were also observed in individuals with traumatic brain injuries (Hurt et al., 1998), Huntington's chorea (Thaut et al., 1998) as well as in healthy individuals (Thaut et al., 1992). These findings have been replicated and extended by numerous research groups (Ford et al., 2007; Spaulding et al., 2013; deDreu et al., 2012) and nowadays RAS is established clinical practice in the rehabilitation of patients affected by motor disabilities.

Rhythmic entrainment was first observed in gait and lower limb movements, but was later applied also to the recovery of upper-limb functions. In order to reproduce the beneficial effects observed in locomotion, discrete arm and hand movements have been turned into fluid, cyclical movements that could be matched to rhythmic cycles. Despite the fact that recovery of arm function is more challenging than gait rehabilitation, the attempts to apply RAS in the rehabilitation of arm movements have shown some favourable results. In stroke patients, the arm trajectory during reaching movements became more consistent after rhythmic training (Thaut et al., 1998). Several other studies have examined the benefits of RAS on upper limb movements, with a focus on hemiparetic stroke rehabilitation (Luft et al., 2004; McCombe-Waller et al., 2006; Schneider et al., 2007; Altenmueller et al., 2009; Malcolm et al., 2009; Grau-Sanchez et al., 2013). The effect of RAS-based rehabilitation is surprising, but much still needs to be clarified. First of all, it is important to examine what type of movements are most affected by the setting of auditory-motor associations. A clear mathematical classification of rhythmic movements based on an analysis of the movements' kinematics would serve this aim and would help provide a selection of rehabilitation exercises and practices. Second, although rhythmic entrainment has been extensively examined via clinical studies, the neuroanatomical and functional knowledge about the brain regions involved in rhythmic processes is still limited. Knowing what brain structures allow auditory-motor synchronization, would help individuate those cases that would maximally benefit from RAS therapy.

Chapter 2. Cerebellum

The cerebellum is suggested to be a key structure in the study of time perception (Ivry, 1996; 1997; Grube et al., 2010; Teki et al., 2011) and auditory-motor synchronisation (Ivry & Keele, 1989; Spencer et al., 2003; Stoodley & Schmahmann, 2009). However, the cerebellum, like any other structure in the brain, does not work in isolation, but as part of a larger system of interconnected regions (Grube et al., 2010; Teki et al., 2012). For this reason, at least in principle the best approach would be to study the brain as a whole. In practice, however, a modular approach is often taken, with the intent to study the processing specific to a certain brain region. In my work I have adopted a modular approach and have directed my effort to examine the role of the cerebellum in auditory-motor synchronisation, motivated also by the fact that the cerebellum has often been neglected in fMRI studies (see **Chapter 3**, **Section 3.2.1**). Written with the intent to provide an overview on the main characteristics of the cerebellum, **Chapter 2** includes a description of cerebellar anatomy, function and dysfunction.

2.1 Microstructure

The cerebellum is a structure at the back of the brain. Externally it is made of a laminated cortex, whose gyri, or *folia*, are highly convoluted and are separated by parallel ridges, or *fissures*, that run transversely and can be seen on the surface. One of the characteristics of the cerebellum is that the neuronal organization of the folia is relatively invariant (see **Figure 2.1**).

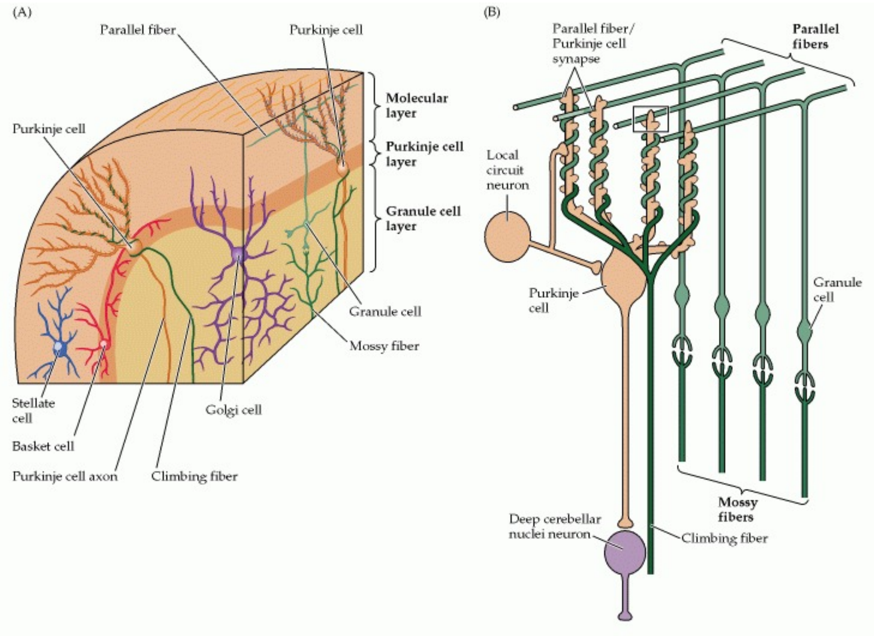

Figure 2.1 *Schematic representation of neurons and circuits of the cerebellum. Figure taken from Purves et al., 2011.*

The folia are made of three neuronal layers. From the surface down there are the molecular layer, the Purkinje layer and the granule layer. Purkinje cells, located in the namesake layer, are the largest neurons in the brain and have branched dendrites that extend upward into the molecular layer. It is estimated that each Purkinje cell receives up to 80000 synapses from t-shaped parallel fibres and that each paraller fiber reaches tens of thousands of Purkinje cells. Parallel fibers originates from the granular cells in the lower layer which in their turn receive excitatory input from non-cerebellar regions. The activity of each Purkinje cell is modulated by multiple synaptic contacts with individual climbing fibers and by inhibitory closed-loop connections with basket cells and stellate cells, interneurons that have their body in the molecular layer. Moreover, Purkinje cells send inhibitory signals to the deep cerebellar nuclei, a cluster of cells embedded in the white matter at the core of the cerebellum. Any output from the cerebellum comes from Purkinje cells and is inhibitory. Any input to Purkinje cells is conveyed by climbing and parallel fibers and is excitatory. Climbing fibres originating in the inferior olive synapse directly with 7-15 Purkinje cells, while each Purkinje cell is contacted by only a single climbing fibre. Mossy fibres do not contact Purkinje cells directly, but their axons synapse with densely packed granule cells and Golgi cells. Axons from the granule layer extend to the Purkinje cell through parallel fibers.

2.2 Anatomical subdivisions

At a macro-structural level, the cerebellum, like the cortex, consists of two hemispheres, symmetrical along the sagittal plane. The cytoarchitecture of the cerebellum is invariant and does not provide anatomical and functional subdivision as is the case for the cerebral cortex. For this reason, the gross anatomy of the cerebellum was described in terms of phylogeny. The cerebellum was divided into *cerebrocerebellum*, *spinocerebellum* and *vestibulocerebellum*, according to phylogenetic criteria, from the oldest to the newest structures. Based on gross anatomy, two fissures deeper than the rest divide the cerebellum into three main lobes (see **Figure 2.2**).

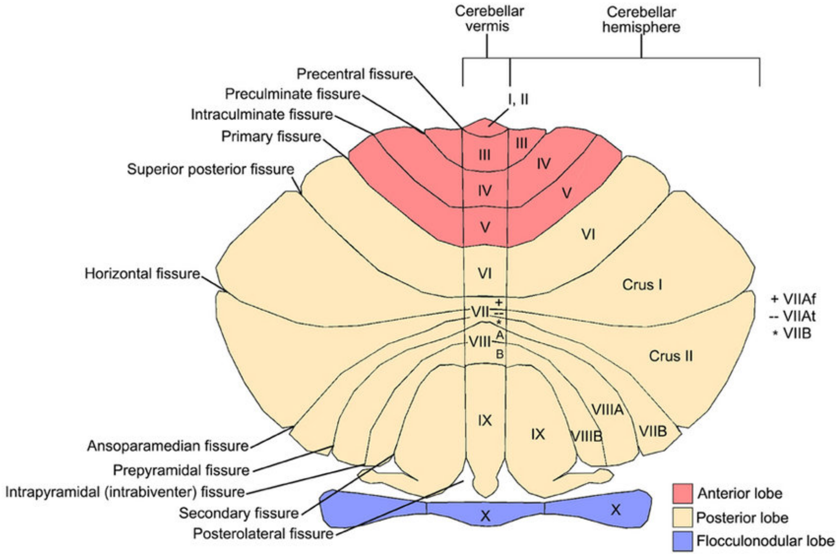

Figure 2.2 *Cerebellar gross anatomical subdivisions, based on major fissures. The flattened cerebellum shows the anterior lobe (red; lobules I-V), the posterior lobe (cream; lobules VI-IX), and the flocculonodular lobe (purple; lobule X). Figure and caption taken from D'Mello & Stoodley, 2015.*

The *primary fissure* separates the *anterior* from the *posterior lobes*. These lobes taken together are known as the *corpus cerebelli*. The *posterolateral fissure* separates the corpus cerebelli from the *flocculonodular* lobe (consisting of the flocculus and nodule). Furthermore, the cerebellum can also be divided longitudinally into a *medial* zone (or *vermal*), *paramedial* (or *paravermal*) and *lateral* portion. A larger set of fissures is conventionally used to subdivide the cerebellum into ten lobules, using a numerical terminology: lobules I-V in the anterior portion, lobules VI-IX in the posterior portion and lobule X in the flocculonodular lobe. Lobule VII is further subdivided into Crus I, Crus II and VIIB in the lateral hemispheres, and VIIAf, VIIAt and VIIB in the vermis, while lobule VIII is further subdivided into VIIIA and VIIIB.

2.3 Relay nuclei

The cerebellum receives direct input from the spinal cord and the vestibular system. Cerebral and spinal connections with the cerebellum are otherwise mediated by the pontine, the precerebellar, the olive and the deep cerebellar nuclei. The pontine nuclei are the main relay station from cortical input to the cerebellum, mainly from frontal and parietal regions. The inferior olive is a relay station for a variety of convergent inputs coming from the spinal cord, the motor cortex, the superior colliculus, the trigeminal nuclei and the vestibular nuclei. The deep cerebellar nuclei, a cluster of cells embedded in the white matter at the core of the cerebellum, and the vestibular nuclei, analogous structure in the brain stem. Through the deep nuclei, dentate, interposed (emboliform and globose) and fastigial, the cerebellum receives input from and projects to distinct cortical areas, through afferent and efferent projections that run in parallel and form a closed-loop architecture. This closed-loop architecture is a fundamental feature of interactions between the cerebellum and the cerebral cortex.

2.4 Cerebellar peduncles

The cerebellum is well connected to the cortex and the spinal cord through three large fibers tracts, organized in pairs of peduncles. The superior peduncles (or *brachium conjunctivum*) are made primarily of efferent fibers that pass through the thalamus and the red nucleus, the middle peduncles (or *brachium pontis*) are made of afferent fibers that originate in the pontine nuclei, while the inferior peduncles (or *restiform body*) contain both afferent and efferent fibers that connect the cerebellum to the vestibular nuclei, the inferior olive, the reticular formation and to several other regions of the tegmentum. Each peduncle contains a massive number of projections. The middle is the largest peduncle and is estimated to contain around 20 million axons, against about one million axons both of the optic nerve or the pyramidal tract. As a result of this, there are far more fibers entering the cerebellum than there are leaving it, with an estimated ratio of 40:1 between afferent and efferent (Colin et al., 2002).

2.5 Afferent and efferent projections

A structure can also be described in terms of its afferent and efferent connections. The lateral cerebellum sends efferent projections to the dentate nucleus via the pontine nuclei, which reach the contralateral cerebral hemispheres via the thalamus, forming the cortico-ponto-cerebellar pathway via the middle cerebellar peduncle. This pathway is instrumental to the regulation of highly skilled movements. The lateral cerebellar hemispheres also form a closed-loop with the ipsilateral red nucleus, located in the rostral midbrain, and the inferior olive, a relay structure in the medulla. This cortico-olivary pathway is thought to have modulatory and adaptive function instrumental to learning.

The medial part of the cerebellum is the only part that receives input from the spinal cord, and thus is named the *spinocerebellum*. The medial part of the spinocerebellum, the vermis, via the inferior cerebellar peduncle, synapses on the fastigial nucleus and is connected via the brainstem to the limb portions more proximal to the body midline, while the lateral part, the paravermis, projects to the interposed nucleus and reaches the distal portions of limbs. The vermis receives proprioceptive signals that originate from the muscle spindles and Golgi tendon organs, and cutaneous information from other mechanoreceptors via interneurons in the spinal cord; it also receives proprioceptive signal from the face via the trigeminal cranial nerve and the mesencephalic nucleus. Moreover, the cerebellum projects to the dorsal nucleus of Clarke in the spinal cord, through the spinocerebellar tract. Spinocerebellar pathways are fundamental to the coordination of limb movements. The spinocerebellum contains a somatotopic organization of sensorimotor inputs, analogous to the organization found in S1, even though the areas of the body surface in the cerebellum are fractured into multiple distinct clusters (Adrian, 1943; Snider & Stowell, 1944; Grodd et al., 2001; **Figure 2.3**).

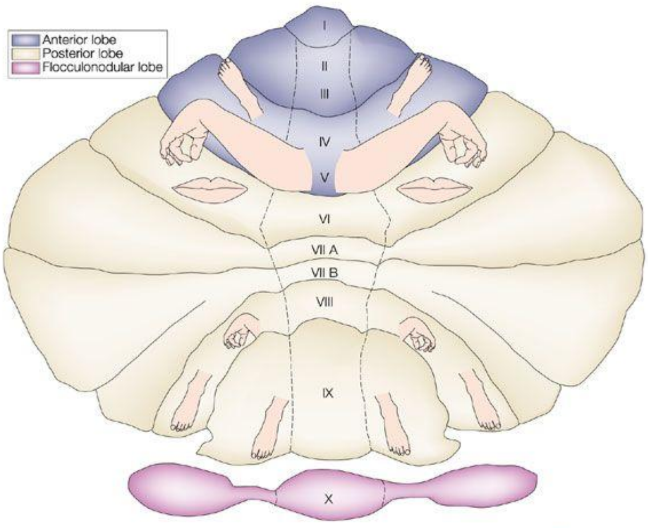

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Figure 2.3 *Somatotopic representations of hands, arms, feet, and lips in the cerebellum, according to the sensorimotor mapping proposed by Grodd et al., 2001. Figure taken from Manni & Petrosini, 2004.*

The spinocerebellum not only receives proprioceptive and somatosensory, but also labyrinthine, visual and auditory input (Adrian, 1943; Snider & Stowell, 1944). Visual and auditory association areas in the posterior parietal and temporal lobe respectively project to the vermis via the pontine nuclei. The vestibulocerebellum, located at the base of the cerebellum and comprising the flocculus and the nodulus lobes, receives vestibular input from the semicircular canals in the inner ear and projects to the vestibular nucleus in the brain stem. This region is involved in the control of axial muscles to maintain balance and posture and in the maintenance of muscle tone. The vestibulocerebellum is also connected to the visual cortex and the superior colliculi, via the pontine nuclei and serves the function of visual tracking and oculomotor control.

2.6 Cerebellar functions

A classical view conceives the cerebellum as primarily involved in motor functions. Each cerebellar hemisphere, in fact, receives exteroceptive and proprioceptive input from the ipsilateral hemifield of the body and is connected via closed-loop circuits to the contralateral primary motor (M1) and premotor cortices (PMC), the contralateral primary and secondary somatosensory cortices (S1 and S2) and the spinal cord. However, experiment using neurotropic viruses and transneuronal tracers have shown that the cerebellum is also connected to many other non-motor regions in the prefrontal and parietal cortex, as well to the basal ganglia. In particular, the projections shown by neuroanatomical studies using transneuronal virus tracers indicates that subcortical structures are also part of a densely interconnected network. For example, the cerebellum projects to the striatum (caudate and putamen) of the BG via the dentate nucleus (Hoshi et al., 2005), while the cerebellar cortex receives projections from the subthalamic nucleus of the BG (Bostan et al., 2010). The functional relevance of these non-motor connections, however, is currently unknown. Cerebellar motor regions can be found in the anterior lobe, lobules III-VI, and in the posterior region, lobules HVIIB and HVIII, and have their counterpart in the dorsal part of the dental nucleus, which is connected to M1 and to premotor areas, unlike the ventral region, which is connected to the prefrontal cortex (Dum & Strick, 2003). Sensorimotor somatotopic representations can be found in lobules II-V and VIII-IX for the lower limbs and V/VI and VIII for the upper limbs and lobules VI and VIII for the face.

Three main functions have been attributed to the cerebellum. First, the cerebellum is supposed to be involved in learning new movements and adapting them to a constantly changing sensory environment (Martin et al., 1996; Chen et al., 2005; Morton & Bastian, 2006; Tseng et al., 2007; Golla et al., 2008). More specifically, the cerebellum is thought to be involved in prediction and learning through experience, and is considered to carry out "state estimation" or estimation of current limb positions, which would be at the basis of reaching behaviour (Miall et al., 2007). Second, the cerebellum is thought to be involved in coordinating movements of multiple joints into a coherent action, a function that is also fundamental to reaching and grasping behaviour. Third, the cerebellum is supposed to work as a timing device, which would time movements' duration. The cerebellum has been proposed to be a key structure of the sub-second timing system (Ivry, 1996, 1997). As a grounding for this hypothesis, cerebellar lesions can lead to deficits in motor timing, measured as increased temporal variability in the execution of periodic but discontinuous movements (Ivry & Keele, 1989; Ivry et al., 1988; Spencer et al., 2003), and in non-motor timing of single intervals in the order of hundreds of milliseconds (Casini & Ivry, 1999; Teki et al., 2011; but see also Gibbon et al., 1997). Furthermore, a cerebellar lesion can lead to an impairment in the temporal properties of the eyeblink conditioning (Gerwig et al., 2003).

Even though the present work mainly focuses on this last function, an overview of all functions is necessary when studying motor control. A glance into cerebellar functions can be gained by examining motor behaviour in patients with focal cerebellar lesions. In the next section, a qualitative characterization of the dysfunctional cerebellum is presented.

2.7 Dysfunctional cerebellum

A Stroke, a tumour, a viral infection or a genetic degeneration that involve the cerebellar system can all result in cerebellar dysfunction. The most widely known hallmarks of cerebellar dysfunction are a loss of sensorimotor coordination, an inability to maintain posture and balance, slurring of speech (or *dysarthria*) and a nystagmus of the eyes. In the 20th century the signs of cerebellar dysfunction in humans was accurately and systematically portrayed by the British neurologist Gordon Morgan Holmes (Sack et al., 2018). Holmes's work is exceptional and still relevant today, primarily thanks to the large number of cases of cerebellar dysfunction he examined during the course of his career. Although Holmes had seen a number of patients with cerebellar tumour before the First World War (25 cases), it was during the war, while volunteering for service with the British medical corps that he had the chance to observe the largest number of cases of cerebellar dysfunction (nearly 70), mostly young adults with a focal lesion caused by gunshot injury. While working in France as a military doctor, Gordon Holmes observed the effects of acute cerebellar injury in the early stages. After his return to England he was able to follow up some of his patients and re-examine them in later post-injury stages. The result of Holmes' observations, first presented during the Croonian lectures given in June 1922 before the Royal College of Physicians of London, were published in The Lancet in the same year. In his inquiry into cerebellar functions, Holmes observed and analyzed the signs of cerebellar dysfunction, and worked on the localization of function in the cerebellum. The method adopted in his study, the *light-line registration*, consisted in attaching light bulbs to the moving limbs and in recording the movements photographically. In order to identify signs of dysfunctional behaviour, Holmes focused on the patients with lesions restricted to one cerebellar hemisphere and compared movements performed between the body limbs ipsilateral and contralateral to the lesion.

As Holmes reported, often in the earlier stages unilateral patients experience a weakness of the limb ipsilateral to the lesion, as a result of reduced force in muscle contraction, a sign called *asthenia*. Muscles at rest are also floppier and less elastic than they used to be, due to a decrease in muscle tone or *hypothonia*. Holmes observed that asthenia and hypothonia are more pronounced during the acute stage of the injury and that, depending on the site and the severity of the lesion, can disappear in later stages. Instead, chronic degenerative diseases of the cerebellum are less likely to produce changes in tone. Hypothonus is responsible for the pendular knee jerk, where after tapping the patellar tendon, the leg swings forward and backward several times, due to reduced resistance from the thigh muscles. Moreover, In case of unilateral lesion, when the limbs are held in a position against the pull of gravity, the affected side of the body fatigues more quickly than the intact side (*fatigability*) and as soon as the muscles begins to tire from holding the static position, often an irregular tremor develops in the affected limb (*static tremor*). Another sign described by Holmes in his lectures is the *rebound phenomenon*, a reflex he first reported together with Thomas Grainger Stewart (Stewart-Holmes maneuver or Stewart-Holmes test, Sack et al., 2018) and later mentioned in the Croonian lectures: "If the resistance that effectively prevents a movement of a normal limb in response to a strong voluntary effort be suddenly released, the limb, after moving a short distance in the desired direction, is arrested abruptly by the action of the antagonist muscles, or it may even jerk back or rebound. This sudden arrest fails frequently in cerebellar disease" (Holmes, 1922a; p.146). After asking a patient to pull his hand over his mouth, while holding the patient's arm by grasping it at the wrist, Holmes observed: "when the grasp is suddenly relaxed the hand of the affected side swings violently towards his face or shoulder, and if the limb be very hypotonic, the elbow may be at the same time jerked off its support with the result that the arm may be flung above his head." This difficulty described by Holmes in arresting passive movements is consistent with a slowness in muscle contraction and relaxation that becomes evident when comparing the opposite body limbs: "If a patient with a unilateral cerebellar lesion be asked to grasp with his two hands an object equidistant from them, or to bring his two forefingers to his nose or to his ears, the homolateral limb usually arrives at its aim later than the normal" (Holmes, 1922b; p. 149). By looking at the graphic recordings of arm movements performed simultaneously with the affected and the intact arms, Holmes noticed that "the (muscle) contraction starts later and the power is developed more slowly" in the affected limb (Holmes, 1922b; p. 149). Moreover, the attempt to execute continuous movements, especially when performed slowly, often results in discontinuous muscle contractions that give an intermittent and jerky look to the movements, even when attempting to keep the movements smooth.

Holmes also described *dysmetria*, a tendency to overshoot or undershoot a target when trying to point at it or reach it, a sign previously reported by the French neurologist Joseph Jule François Félix Babinski (1913) and first observed by Huppert in 1878 (Babinski, 1913): ”In attempting to pass his nose the patient’s finger may pass it and strike his cheek violently, and the same may occur in bringing his finger to any point outside him […]. Voluntary movements are less commonly arrested before their arm is reached, but it sometimes happens that in approaching his nose or any other point the finger stops some distance short of it, and is then brought to it by a second movement or by a series of jerks” (Holmes, 1922b; p. 149). Dysmetria is often associated with errors in direction, where the limb abruptly deviates from the line of movement and is broken into an irregular zigzag. According to Holmes, when patients execute fast movements, they are more likely to make hypermetric errors, due to the fact that the limb acquires an abnormal velocity in the later phase of movement execution and that movement termination is delayed compared to the intact limb. Slower movements, instead, are more often fractured into series of irregular jerks, so that the slower the movement the more fragmented and irregular. Holmes has also confirmed *adiadochokinesis*, a sign previously described by Babinski (1902) that consists in the inability of cerebellar patients to execute rapid alternating movements. An invariable rule that applies to all cerebellar signs is that irregularity of an action increases with the number of joints or loose limb segments involved in the action. The cerebellar signs reported by Holmes can be found in contemporary textbooks.

Experimental Research

Chapter 3. General Methods

3.1 Transcranial Magnetic Stimulation (TMS)

TMS is a non-invasive method that allows one to interfere temporarily with the activity of a brain region. TMS has been used to study intracortical facilitation and inhibition and cortico-cortical interactions, to map motor cortical output, to measure motor conduction times, to examine any impact on behaviour, and as a treatment for psychiatric and neurological disorders (Rossi et al., 2009; Rossini et al., 2014). The operating principle of TMS is electromagnetic induction, first discovered by Michael Faraday in 1831 and later generalized into the Maxwell-Faraday equation. The two main phenomena of electromagnetic induction are the induction of an electric flow in a nearby conductor by a time-varying magnetic field and the induction of a magnetic field by a time-varying electric flow. In TMS, electric charge stored in a capacitor is discharged abruptly, resulting in a strong electrical current. This current passes through a stimulator coil and induces a magnetic pulse in the vicinity of the coil. The magnitude of the induced magnetic pulse is proportional to the rate of change of the electric current in the coil. The magnetic pulse in turn induces an electric field inside a brain region near the point of the scalp in contact with the coil. TMS pulses can be delivered one at a time (*single-pulse* TMS or sTMS), in pairs and with a slight time offset, this either on a same or on two different locations (*paired-pulse* TMS or pTMS) and in trains of different frequencies and patterns (*repetitive* TMS or rTMS). In particular, single-pulse TMS can be used to study brain-behaviour relations as a function of time. It is also possible to stimulate the brain via transcranial electrical stimulation (TES), but this inadvertently activates skin receptors and pain fibres to a greater extent compared to TMS, thus resulting in increased discomfort for the participant. The most common TMS coil has a figure-of-eight shape and is made of two circular wings. The figure-of-eight coil has better focality, compared to circular coils. TMS coils can vary in diameter (e.g. 40, 50, 75, 100, 130 mm) and can either be flat or have angled wings (e.g. double-cone coil, batwing coil). As a rule of thumb, larger, angled coils can reach deeper brain regions, at the expense of reduced focality and therefore can be used to stimulate deeper regions. The double-cone coil (130 mm diameter, **Figure 3.1**), for example, has been shown to be more effective than the figure-of-eight or the batwing coil when stimulating the cerebellum (Hardwick et al., 2014).

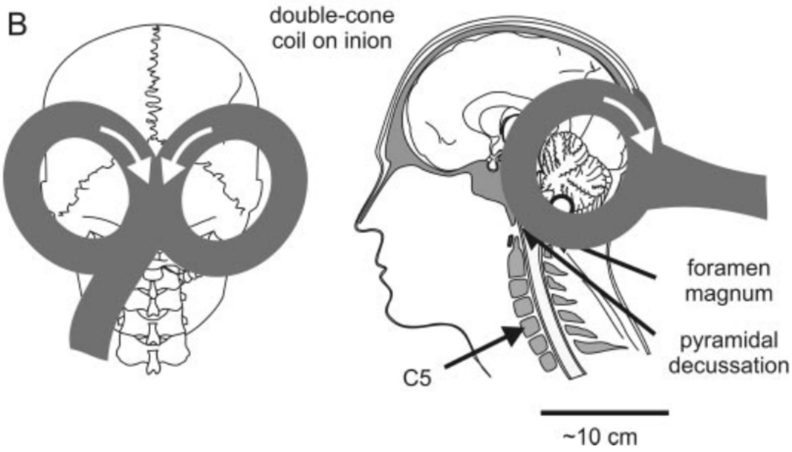

Figure 3.1 *Schematic representation of double-cone coil. This coil was used to effectively stimulate the cerebellum and the corticospinal tract. Adapted from Taylor & Gandevia, 2004.*

3.1.1 Motor evoked potentials (MEPs)

When TMS targets the primary motor cortex, a brain region that projects directly to the spinal cord, the action potentials elicited in the brain by the TMS pulse travels through the corticospinal tract, all the way to the periphery of the body. This corticospinal volley may be felt as a tingling sensation and is sometimes accompanied by a visible muscle twitch. When muscle activity is monitored with electromyography (EMG), a peak in the signal or motor evoked potential (MEP) can be measured after the TMS pulse delivered on the hemisphere contralateral to the limb monitored.

The amplitude and the latency of MEPs vary based on the intensity of stimulation, the muscle monitored, and the level of excitability of the cortico-motor pathway, and can be used to measure the speed of conduction. More specifically, the amplitude of MEPs results from the summation of a series of descending cortico-spinal volleys with different generators. Distinct volleys can be measured with epidural recordings from the spinal cord when a single electrical stimulus is applied at threshold to the surface of the motor cortex. The first volley is called direct (or D-) wave and is elicited by direct activation of pyramidal tract axons. With increasing stimulus intensity, later waves called I-waves come to follow (i.e., I1, I2 and I3 in order of latency). I-waves are thought to result from trans-synaptic activation of pyramidal tract neurons. Unlike D-waves, I-waves integrate the contribution of cortico-cortical afferents (e.g., premotor cortex; supplementary motor area).

The latency of MEPs reflects the conduction time for such cumulative neural impulse to travel from the cortex to peripheral muscles. As a rule of thumb, MEPs measured from more proximal muscles will have shorter latency than those recorded from more distal muscles (see **Figure 3.2**).

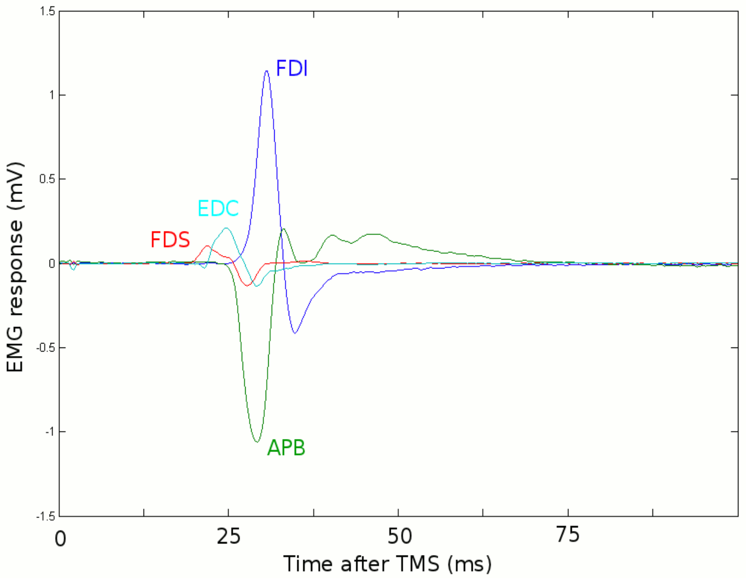

Figure 3.2 *MEPs measured from Flexor Digitorum Superficialis (FDS), Extensor Digitorum Communis (EDC), Abductor Pollicis Brevis (APB) and First Dorsal Interosseous (FDI) muscles. Figure taken from HandLab repository.*

3.1.2 Cerebellar TMS

The human cerebellum can be stimulated electrically (Ugawa et al., 1991) and magnetically (Ugawa, 1995); cerebellar stimulation has been shown to alter motor cortex excitability. For example, a TMS pulse delivered over the posterior fossa (PA), with the coil centred over the inion, can reduce MEPs elicited by a second pulse over the contralateral motor cortex, delivered 5-7 ms after cerebellar stimulation (Ugawa, 1995; Matsunaga et al., 2001). Despite the encouraging results of these studies, a consensus on the effectiveness of cerebellar TMS is still to be reached, due to the fact that this technique is prone to confounds. Cerebellar stimulation, in fact, can simultaneously activate many other structures in the brainstem (Fisher et al., 2009). Another concern is that cerebellar TMS can stimulate afferent fibres in the posterior neck, influencing the excitability of the corticospinal tract, rather than directly affecting cerebellar structures and its projections to the motor cortex (Fisher et al., 2009). Notice that when the coil is centred on the inion, for example, its wings are in contact with the back of the neck (**Figure 3.1**). Furthermore, cerebellar TMS does not have a direct measurable outcome, therefore selecting an appropriate intensity of stimulation is not straightforward. In principle, an appropriate intensity of stimulation should be set at a level high enough to reach and stimulate cerebellar grey matter, but low enough to avoid brainstem structures, while limiting the stimulation of peripheral structures. The classical method for setting stimulation intensity in TMS studies is as a percentage of participant's motor threshold, which is defined as the minimal intensity required to elicit MEPs > 50 µV with 50% probability (out of at least 10 trials), either in a fully relaxed muscle (resting MT) or in a muscle maintained at isotonic contraction (isotonic or 'active' MT, Rossini et al., 1994). The relationship between motor cortex and cerebellar excitability, however, is not obvious, so this method does not provide a good standard practice when stimulating the cerebellum. An alternative method is to measure a threshold for direct corticospinal tract (DCT) stimulation by placing the coil over the inion and stimulation during tonic muscle contraction, which increases the chances of detecting a corticospinal tract volley, compared to stimulation of a relaxed muscle. Previous work has then set the intensity of stimulation to 5–10% MSO below this DCT threshold, so as to limit the effect of TMS on the spinocortical tract (Ugawa et al., 1994, 1995; Matsunaga et al., 2001). This second method was adopted in the TMS study reported in **Chapter 5**.

To sum up, cerebellar TMS has several limitations: 1) it can inadvertently activate structures in the brainstem, thus requiring extra caution when interpreting the result; 2) it can activate head and neck muscles, which can result in muscle twitches and altered corticospinal excitability; 3) it requires high stimulation intensities to be effective (i.e. at least 60% of maximum stimulator output – MSO, Hardwick et al., 2014), thus increasing the risk for the participant; 4) it is accompanied by a loud clicks in the range 75–100 dB in intensity, thus limiting its use in auditory studies; 5) it can cause great discomfort to the participant, for all the reasons mentioned above, therefore an extra effort has to be made, in order to match in discomfort critical and control conditions, because the discomfort alone can worsen task performance (Meteyard & Holmes, 2018).

3.2 Functional Magnetic Resonance Imaging (fMRI)

In magnetic resonance imaging (MRI), a strong magnetic field is used to obtain an image of the biological tissue. MRI scanners used on humans for research use have field strength between 1.5 and 10 Tesla. For comparison, the Earth's magnetic field is approximately 0.00005 T. Magnetic resonance can be used to study only the tissues that have a nuclear magnetic resonance (NMR) property called *spin*[2]. Hydrogen nuclei of water molecules (H2O), which are present in most biological tissues, dominates the signal measured in conventional MRI. In the absence of a strong magnetic field, the spin axes of the protons are oriented randomly and the sum of all their magnetic moments, or *net magnetization*[3], is infinitesimally small. When a strong magnetic field is applied, the spin axes tend to align with the direction of the external magnetic field, for the principle of energy minimization. Each spin wobbles or *processes* around its axis, at a frequency called Larmor frequency, which depends both on the type of nucleus and on the intensity of the magnetic field. When a radio frequency (RF) pulse at the Larmor frequency is applied to a *spin system*[4], the spins' axes can be rotated by a 90° angle, to convert the longitudinal magnetization into transverse magnetization. At first the spins process in phase with each other, but as time passes, the spins progressively dephase; with time the spins recover their longitudinal magnetization and align their axis with the magnetic field. Different types of biological tissue can be resolved based on the *relaxation rates*, the rate at which the spins diphase and reform the net longitudinal magnetization after a RF pulse, which depend on a number of parameters including the degree of water binding within the tissue. Different relaxation processes are described: the *longitudinal relaxation* is the recovery of the net magnetization along the longitudinal direction after a RF pulse described by the T1 time constant; *transverse relaxation* is the loss of net magnetization within the transverse plane due to the loss of phase coherence of the spins and to changes in local field inhomogeneities, described by the T2 and T2* constants. By varying the time periods between RF pulses, called repetition time (TR), and the time between a RF pulse and the start of data acquisition, or echo time (TE), it is possible to build acquisition sequences with different type of sensitivity. For example, sequences with short TR and short TE can be used to resolve the structural properties of biological tissues (e.g., grey matter, white matter, cerebrospinal fluid), while sequences with long TR and medium TE can be used to measure changes in blood oxygenation level in response to the metabolic consumption of active neurons, as an indirect measure of neuronal activity (functional MRI). Functional activation can be monitored also by measuring tissue perfusion and blood-volume changes, but the blood-oxygen-level-dependent (BOLD) contrast, which measures changes in the

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[2] Magnetic nuclei that have both a magnetic moment and an angular moment.

[3] The sum of the magnetic moments of all spins within a volume; this can be represented as a 2D vector with a longitudinal component, either parallel or antiparallel to the magnetic field, and a transverse component perpendicular to the magnetic field.

[4] All spins present in a certain volume.

local concentration of oxygen is the most widely used method. The BOLD contrast relies on the magnetic properties of the iron-containing oxygen-transport protein in the red blood cells: haemoglobin. Deoxygenated haemoglobin has paramagnetic properties that can introduce inhomogeneities into the local magnetic field. The more deoxygenated haemoglobin is in the blood, the faster the transverse relaxation (T2*) and the lower the BOLD signal. Even though the BOLD response is thought to reflect neuronal activity, the link between these two is complex and still in part unclear (Goense & Logothetis, 2010). This relationship was first examined in electrophysiological studies on the visual system of anesthetized and alert monkeys (Logotheti, 2001; Goense & Logothetis, 2008). These studies showed that the BOLD signal was correlated to local field potentials (LFP), and to some extent also to multi-unit and single-unit spiking. However, BOLD responses and LFP were measured also in the absence of spiking, thus indicating that glucose utilization alone can lead to neuronal synaptic activity (Mathiesen et al., 1998; Logothetis et al., 2001; Viswanathan & Freeman, 2007; Goense, & Logothetis, 2008). A clear advantage of fMRI is that, unlike positron emission tomography (PET), it is non-invasive and can be used on clinical or sensitive populations. fMRI has also a higher spatial resolution than MEG, even though its temporal resolution is limited by the nature of the BOLD signal. Spatiotemporal resolution of fMRI has improved greatly since the introduction of this technique in the early 1990s, thanks to the optimization of pulse sequences and resonators, the use of higher magnetic fields, and the invention of methods for parallel imaging (Logothetis, 2008). However, the limitations of fMRI have neural origins and are unlikely to be overcome by further technological advancement (Logothetis, 2012). As Logothetis suggested, it is therefore important to keep in mind what we can and what we cannot do with fMRI, in order to design and analyse studies, and interpret the results correctly. For example, fMRI cannot distinguish task-related activation and activation in response to neuromodulatory effects, like attention or arousal, or between excitation and inhibition. Furthermore, differences in magnitude of the BOLD response do not necessarily reflect the differential involvement of a brain region in different tasks, or the involvement of separate regions in the same task. BOLD responses, in fact, are sensitive to the size of the population of neurons activated by a task and the sparsity of this population is likely to vary in space and time. Despite these limitations, fMRI has been used to successfully detect task-related changes in BOLD signal, relative to task-unrelated activity. It has also been used to examine task-unrelated fluctuations in the BOLD signal that allow us to study the functional organization of brain networks (resting-state fMRI).

3.2.1 Functional MR imaging of the cerebellum

Imaging the cerebellum with functional magnetic resonance imaging (fMRI) is hard. Even though the cerebellum was first studied with functional imaging almost 35 years ago (Fox & Raichle, 1985), showing activation in response to eye and finger movements, technical challenges specific to this structure have slowed down progress.

When scanning at the low to medium field intensities of 1.5–3 T, standard echo-planar imaging (EPI) sequences do not allow whole brain coverage with good isotropic spatial and temporal resolution (e.g., < 2.5 mm and 3 seconds respectively). The majority of researchers have worked around this problem by limiting the region of acquisition to the cerebrum, leaving the cerebellum out of the picture. In other cases, different strategies have been adopted to retain the cerebellum in the scan; these largely depended on the locations of all other regions of interest to the study, relative to the cerebellum. One solution consists in covering only the lower part of the brain, leaving out the top (e.g., Wiestler et al., 2011); a second solution involves covering the whole brain, but with sparsely distributed axial slices (e.g., Miall et al., 2001). It is important to acknowledge that typically axial or axial-oblique slices are commonly used, even though coronal and sagittal acquisitions can be valid alternatives. One issue to keep in mind is that the direction of any magnetic field-induced geometric distortions will depend on the slice type. For example, coronal slices show less dropouts and distortions in the frontal and temporal lobes, compared to axial slices, but generally exhibit a loss of symmetry between left and right hemispheres, which can be disconcerting ("out of sight, out of mind"). Besides, if the intent is to cover as much brain as possible, coronal and sagittal slices are not ideal, because many more slices are required to cover the same volume with a given repetition time (TR). However, if the regions of interest are distributed on a vertical or oblique line, with limited spread from front to back, near-coronal or sagittal slices provide better coverage. An optimal choice will depend on the specifics of the study.

A second challenge to imaging the cerebellum is increased physiological artefacts from cardiac and respiratory cycles in this structure, compared to the rest of the brain. The cerebellum, in fact, has a dense vasculature. Besides, demanding tasks (both motor and cognitive) are often associated with an increase in heart rate, therefore, changes in fMRI signal introduced by cardiac noise can be misinterpreted as task-related changes (Van der

Zwaag et al., 2015; Diedrichsen et al., 2010). The cerebellum is also closer to the thoracic cage than the rest of the brain, with the result that fMRI signal will encode the rise and fall of the chest. During an fMRI session, physiological noise is usually dealt with by recording cardiac and respiratory cycles with pulse oximeters (or electrocardiograms, ECG), and pneumatic belts; these recordings are then used to remove any artefacts from the fMRI signal.

As a third concern, the small size of the functional regions in the cerebellum leads to errors in normalisation to the MNI template, often the reference atlas. When normalizing the brain to the MNI atlas, the cerebrum drives the realignment, since cerebellum is smaller in size and the MNI template provides poorer contrast for its structures. As a result of this, the localization of cerebellar lobules based on MNI coordinates is subject to error (Diedrichsen et al., 2010). Unfortunately, normalisation is a necessary step for classical group analysis in MRI. In order to overcome this limitation, a population template and a normalisation method, the spatially unbiased infratentorial template (SUIT), have been developed (Diedrichsen et al., 2006).

To sum up, this section highlighted some of the critical aspects that need to be taken into account when imaging the cerebellum; when using functional MRI, specific imaging and analysis techniques must be used. Even though standardized practices exist for artefact removal and normalisation, there is no golden rule for selecting an appropriate acquisition sequence, since this choice is highly dependent of the research objectives. In the context of the thesis, cerebellar fMRI has been used in the experimental work presented in **Chapter 6**.

3.3 General apparatus and set-up

This section includes a description for the apparatus and set-up in common to **Chapter 5** and **Chapter 6**.

3.3.1 Electromyography (EMG)

Behavioural Sessions. The EMG signal was sampled from bipolar surface electrodes at 4 kHz with a range of 5 mV, filtered with analogue low-pass filter of 500 Hz and high-pass filter of 10 Hz (PowerLab 16/30, AD Instruments, CITY) and amplified with Dual BioAmp (AD Instruments). The signal was acquired with the software LabChart running on a Windows PC.

fMRI Session. The EMG signal was sampled from bipolar MRI-compatible surface electrodes at 5 kHz with hardware filter set to record in the range 0.016–250 Hz with a roll-off of 30dB/octave at high frequency. The signal recorded from the active electrodes was fed into an MR-compatible amplifier (BrainAmp ExG, Brain Products, Munich, Germany), placed at the foot of the scanner bed on a foam pillow, in order to reduce the effect of vibrations on the electronics. Electrodes impedance before entering the scanner was kept at 25 kΩ. All electrode leads were twisted to minimize wire loops and the consequential differential effect of the magnetic field on the leads (van Rootselaar et al., 2007). The EMG signal was recorded with BrainVision Recorder. BrainVision Analyzer was used for scanner artefacts removal.

3.3.2 Motion tracking

Finger movements were recorded with a Polhemus Liberty Long-Range (Polhemus, Colchester, VT, USA) magnetic tracking system, sampling at 240 Hz. Each motion tracker could record the 6D-position, including 3 translations and 3 rotations. Signal acquisition with Polhemus was controlled by a custom LabView program (version 2017) running on a Windows PC.

3.4 Measures of auditory-motor synchronization

This section provides an account of the main measures of auditory-motor synchronisation performance and other movement kinematics, reported in **Chapter 5** and **Chapter 6**. Auditory-motor synchronisation was assessed with variations of the finger-tapping task. In the standard version of this task, participants are required to oscillate their finger up and down at a predetermined rate, aligning the taps with the presentation of an external auditory pacing stimulus. The measures reported below were derived from the position of the index finger, recorded with motion tracking during the standard version of the finger-tapping task. However, a similar procedure was applied also to periodic circle drawing movements studied in **Chapter 6**.

3.4.1 Pre-processing of the position signal

The data exported from LabChart and LabView were stored in separate data files and were re-aligned in time based on a digital trigger stored in both files, indicating the start of sampling of position with Pohlemus. The position signal along the vertical axis was then detrended with linear least squares fitting (scipy.detrend from SciPy library) to remove drifts caused by slow changes in the participant's forearm position. If TMS was applied, the position signal was first despiked with a custom python function, which applied a 3-points interpolation with a cutoff threshold of 2 standard deviations from the mean of the normalized signal (mean [SD] = 0 [1]). This was done to remove any TMS-induced artefacts. Velocity and acceleration were then derived from position. In order to calculate the time of peak of position at full extension and the time of trough of position at full flexion for each movement cycle, local maxima and minima of the vertical position were detected by taking the first- and the second-order derivatives along the vertical axis. The set of local maxima and minima was refined by manually removing any extra values, so that within each movement cycle there was only one minimum and one maximum value. The result of this selection was checked through visual inspection (see **Figure 3.3** for an example).

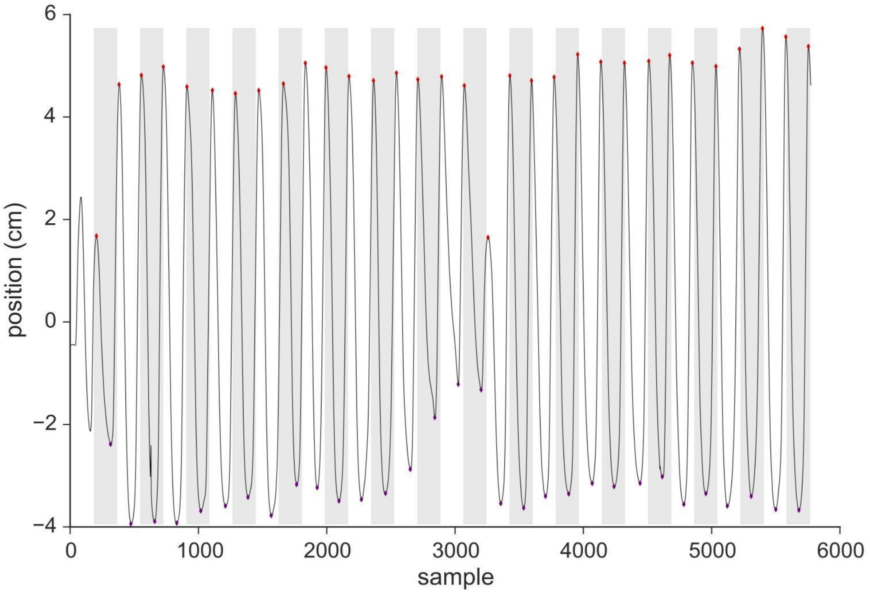


Figure 3.3 *Vertical position of the index finger recorded during one trial, together with maxima (red dots) and minima (purple dots) detected at each tapping cycle. The maxima correspond to the taps and were used to calculate the inter-tap-interval and the negative asynchronies. The edges between the shaded areas in white and grey correspond to the times when the tones were played.*

3.4.2 Inter-tap-interval (ITI)

A measure of auditory-motor synchronization, based on the times between consecutive taps, the ITI was calculated by taking the difference in the time between each consecutive pair of taps in a trial. The series of ITI for each trial were detrended, in order to remove drifts, similarly as in Spencer et al. (2003).

3.4.3 Coefficient of variation of the inter-tap-interval (CoV ITI)

A measure of finger-tapping variability, the coefficient of variation of the ITI was calculated by dividing the standard deviation by the mean of the ITI for each trial. The coefficient of variation was preferred to the standard deviation as an estimate of tapping variability, because it is not affected by differences in the mean across conditions (Spencer et al., 2003).

3.4.4 Negative asynchronies (NAs)

The NAs were calculated by taking the difference in time between each tap and the nearest sound. Sounds were matched to taps in a one-to-one fashion following a sequential order, pairing each sound in the sequence with the closest unmatched tap. When the number of taps exceeded the number of sounds, the unmatched taps were coded as errors.

3.4.5 Mean and peak cycle velocity

Mean and peak cycle velocity were calculated, in order to characterise auditory-motor synchronisation in terms of movements kinematics. These two measures were calculated by taking the mean and the peak of velocity for each upward and downward phase of all cycles of periodic movements, then averaging within cycles and trials, and across trials.

3.5 General practice for statistical testing

In the analysis, whenever Mauchly's test indicated violation of sphericity assumptions, Greenhouse-Geisser corrections were applied. Two-tailed paired Welch's t-tests were applied in post-hoc comparisons: the Welch's t-test was preferred to the Student's t-test, because it does not rely on the assumption of equality of variances, which is often violated in psychological experiments (Delacre et al., 2017). Bonferroni corrections were made to correct for multiple comparisons. The effect sizes reported are Cohen's d (d) and generalized eta-squared (η_G^2).

Chapter 4. Effect of a Regular Context on Duration Perception

This chapter is a report of two behavioural experiments on duration perception, carried out to examine the ability to make temporal judgments in humans, focusing on the effect of a temporally regular auditory context on duration perception. The experiments reported in this chapter have been published (Zeni et al 2018); I acknowledge the co-authors' inputs, which were commenting and editing the manuscript.

4.1 Abstract

In the auditory domain, the perceived duration of time intervals is influenced by background sounds - the auditory context in which the intervals are embedded - even when the background may be ignored. Previous research has shown that a regular context made of evenly spaced sounds improves participants' discrimination of intervals close in duration to the context intervals. These results have been explained in terms of attention and anticipation. The present study reconsiders the effect of context regularity, focusing on the relationships among the intervals in the context and the interval to be estimated. The influence of a regular compared to a non-regular auditory context on interval discrimination was examined with a two-interval forced choice task, which required participants to discriminate between the durations of two time intervals. Duration perception was more precise when the intervals to be discriminated were preceded by a regular compared to a non-regular context. This effect of the regular context, however, was not selective for the duration of the first interval to be estimated, contrary to what suggested based on the available evidence.

4.2 Introduction

The ability to perceive the duration of events in the range of milliseconds to seconds is thought to be fundamental to a number of cognitive abilities, including moving under temporal constraints, speech comprehension, music perception, and music production (Buhusi & Meck, 2005). Duration perception, however, is not always veridical or reliable. It is influenced by auditory context - the presence of irrelevant sounds preceding, overlapping with, or succeeding the target sounds (Barnes & Jones, 2000; Large & Jones, 1999). For example, empty intervals delimited by a marker at the beginning and the end are perceived to last longer than both filled intervals, in which the signal to be judged is continuous, and intervals filled by multiple regularly spaced markers (Buffardi, 1971; Thomas & Brown, 1974, Adams, 1977; Rammsayer & Lima, 1991; Rammsayer & Leutner, 1996). Moreover, intervals interspersed with regularly spaced fillers are perceived as longer than intervals with irregularly spaced fillers (Thomas & Brown, 1974). Interestingly, such distortions are not observed when non-temporal properties of the fillers (e.g., the sounds' amplitudes or frequencies) are made irregular (Horr & Di Luca, 2015).

Other studies have examined the effect of contextual information on the perception of empty intervals and have shown that duration perception measured in a two interval discrimination task was distorted when an interval of short duration preceded the interval to be discriminated, compared to a condition in which a similar distractor was not present (Burr, Della Rocca, Rocca & Morrone, 2013; Karmarkar & Buonomano, 2007; Spencer, Karmarkar & Ivry 2009).

The auditory context has also been shown to systematically influence the perceived duration of single auditory events embedded in the context (Barnes & Jones, 2000; Large & Jones, 1999). This effect is likely automatic, since it has been observed even when participants were explicitly told to ignore the context (Barnes & Jones, 2000; Drake & Botte, 1993; McAuley & Kidd, 1998). When presented with sequences of evenly spaced sounds, listeners were more accurate in judging the duration of tones that end at expected rather than at unexpected points in time (Barnes & Jones, 2000; Large & Jones, 1999). Accuracy in this task followed an inverted U-shaped profile, with the highest accuracy centred on the expected end points, diminishing for sounds presented earlier or later (Large & Jones, 1999). These results provided the grounds of the dynamic attending theory (DAT), which hypothesizes that attention fluctuates periodically over time, and synchronizes with the periodicity of the ongoing auditory stimulation (Barnes & Jones, 2000). In support of DAT, a regular sequence has also been shown to affect judgments of non-temporal stimulus properties, and the typical U-shaped "expectancy profile" has been observed with a pitch identification task (Jones, 2002).

In the present work, the effect of a regular auditory context is re-examined with the intent first to replicate the results of Barnes and Jones (2000), and second to extend them, by focusing on the temporal relationship between the intervals in the context and the first interval to be discriminated, the “reference” interval. The reference interval could either be 100%, 70%, or 50% of the duration of intervals presented in the context. According to the DAT, duration discrimination should benefit maximally from a regular context when the reference interval is equal in duration to the context interval, due to the fact that attention is at its peak when the end marker for that interval is presented. Discrimination of intervals shorter or longer than the context interval, instead, should progressively decrease. In accordance with DAT, we expected to observe the best discrimination with a reference that is 100% of the context interval. Our second prediction is neither part of the DAT nor in contrast with it: a greater effect should be observed with a 50%, compared to a 70% interval, due to the fact that a 50%, unlike a 70% interval, divides the period into two halves, and demarcates an integer subdivision of the rhythmic context. This is despite the fact that a 50%, relative to a 70% interval, is farther from the context interval in terms of absolute duration.

In our first experiment, we examined the extent to which a regular compared to a non-regular context influences the perceived duration of time intervals. We first examined whether discrimination varied across reference intervals of different duration. Second, we examined to what extent any difference in discrimination with regular compared to non-regular context depended on the relationship among the intervals in the context and the first interval to be estimated. More specifically, we examined whether discrimination was best when the interval to be estimated was equal in duration to the context intervals, thereby replicating the experiment of Barnes and Jones (2000).

4.3 Methods

4.3.1 Participants

Twenty-eight participants were recruited. Four were excluded (see below), leaving a sample of 24 participants (mean ± SD age = 22.9 ± 3.0 years, 19 female). Participants provided written informed consent and participated in return for payment (£15). All participants reported normal hearing and no history of audiological or neurological disorder. The study was approved by the research ethics committee of the School of

Psychology at the University of Nottingham (SoPEC 932) and was conducted in accordance with the Declaration of Helsinki (as of 2008).

4.3.2 Apparatus

Auditory stimuli were presented binaurally with PsychPortAudio (Psychotoolbox v. 3, Brainard, 1997; Pelli, 1997) from a MacBook Pro running MacOS X version 10.9.5 using the built-in Core Audio audio device and through headphones (Philips O'Neill SHO9565BK). All stimuli were digitally created with Matlab (Mathworks, Natick, USA) at a sampling rate of 44.1 kHz and 16 bit resolution. Responses were collected with a standard USB computer keyboard. The python package Psignifit 3.0 (Fründ, Haenel & Wichmann, 2011) was used for curve fitting; the free software R (R Core Team, 2016) was used for data analysis.

4.3.3 Stimuli

All auditory sequences comprised series of short sounds of 50 ms interspersed with blank intervals. Each sequence started with a series of low-frequency sounds of 440 Hz, randomly varying in number from 3 to 5, the "auditory context", and was followed by two pairs of high-frequency sounds of 660 Hz. The time interval between the first pair of high-pitched sounds is referred to here as the "reference" interval, while the interval between the second pair is the "comparison" interval. The intervals between the low-frequency sounds in the auditory context could either be isochronous, with a constant duration of 660 ms, or centred on 660 ms and varying randomly by adding a normally-distributed amount of jitter N [0, 100] ms. The duration of the auditory context was comparable between conditions. The reference interval lasted either 660, 462 or 330 ms. The duration of the comparison interval varied according to the method of constant stimuli: the comparison interval was expressed as a percentage of the reference interval and could take one of 10 values, with 5 increments and 5 decrements relative to the reference (± 1%, 3%, 6%, 12%, 30%). Each of the 10 comparison values was presented 10 times in each condition (**Figure 4.1**).

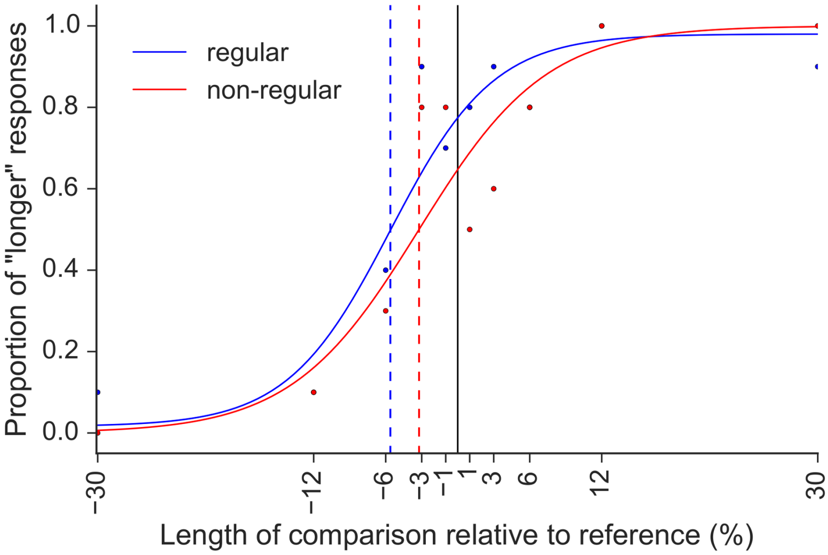


Figure 4.1 *Example of the psychometric functions fitted in experiment 4.1 for participant S9 and 660 ms reference, with regular (blue) and non-regular (red) auditory context. The PSE values (indicated by vertical dashed lines) were expressed as percentage of increase (1, 3, 6, 12, 30 %) or decrease (-1, -3, -6, -12, -30 %) in the length of the comparison relative to the reference interval. In this example, the PSE values of -5.6% measured with regular auditory context indicates that the comparison had to be 5.6% of 660 ms shorter than the reference, to be perceived as of equal length.*

Given that the length of the comparison was proportional to the length of the reference, the difference between reference and comparison intervals in terms of absolute duration was smaller for shorter intervals. According to the Weber-Fechner law (1860), the perceived change in stimuli is proportional to the magnitude of the stimuli. Given that duration discrimination should be proportional to the duration of the reference interval, by adapting the length of the comparison to the length of the reference we expected to increase the sensitivity of our method and allow comparisons across intervals.

4.3.4 Design

Figure 4.2, panel A, illustrates the experimental design. The two factors manipulated were Auditory context (regular, non-regular) and Reference duration (660, 462, and 330 ms, corresponding to 100%, 70%, and 50% of the context interval). The regular auditory context is made of a series of sounds separated by intervals of constant duration; the non-regular context is made of a series of sounds separated by randomly varying time intervals. All participants completed all sessions, and the order of sessions and parts was counterbalanced across participants.

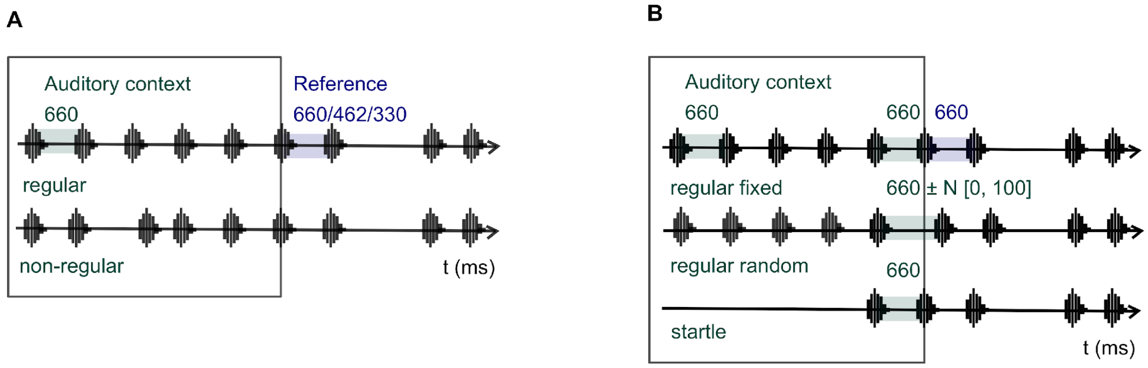


***Figure 4.2** Stimuli of experiment 4.1 (A) and experiment 2 (B): auditory context made of low-frequency sounds (regions surrounded by squares) and two pairs of high-pitched sounds delimiting the reference and the comparison intervals. The variables of experiment 4.1 were Auditory context (regular, non-regular) and Reference (660, 462, and 330 ms). In experiment 4.2 only Auditory context (regular fixed, regular random, startle) was manipulated, while the duration of the reference interval was fixed to 660 ms.*

4.3.5 Procedure

Participants were seated at a table, wore headphones, and listened to sequences of short sounds. Their task was to compare the last two time intervals of each sequence - the ones interspersed between two high-pitched sounds - while ignoring the series of low-pitched sounds presented at the beginning of each trial. Participants were required to say whether the last interval, the comparison, was shorter or longer than the second-to-last interval, the reference. Participants answered by pressing one of two keys on a computer keyboard, and were instructed to respond as accurately as possible. No strict time limit was set for the response. A white noise sound of 100 ms signalled the beginning of each trial; the series of low- and high-frequency sounds began 600 ms later. Reference and comparison intervals were separated by a gap of 1200 ms. The experiment comprised three sessions, one for each reference (660, 462, and 330 ms). The sessions were run on separate days, not necessarily consecutive (M]SD] = 4 [10] days in between). Each session was divided into two parts, one for each Auditory context (regular, non-regular). Each part started with a practice block (20 trials) and included two experimental blocks (2 X 50 trials). The order of parts and sessions was counterbalanced.

4.4 Analysis

The following criteria were set before starting data collection, to determine which data to include in the analysis: for each session, overall percentage correct ≥ 60%; mean percentage correct for the two easiest comparisons (± 12%; 30%) ≥ 85%. Participants who performed below this cut-off in the first session were not asked to participate in the remaining sessions.

The data were fit with psychometric functions. The shape of the function was defined by the parameters "sigmoid" and "core", which were set to "logistic" and "ab" respectively (http://psignifit.sourceforge.net/WELCOME.html). The shape of the function was chosen amongst the many options provided by the toolbox Psignifit, so as to provide the best fit to our dataset. The Psignifit function "BootstrapInference" was used to find the best fit and to estimate the free parameters of the model, alpha and beta, while gamma and lambda were constrained to the range [0, .06], to account for lapses in attention and errors unrelated to the stimulus properties, respectively. Alpha corresponds to the point of subjective equality (PSE), while beta is a measure of the spread of the function and is directly related to the just noticeable difference (JND). The dependent variables of interest in the analysis were the PSE and the JND. The PSE was calculated as the point on the curve corresponding to 50% of "longer" responses; PSE values indicate the amount of increase or decrease in the duration of the comparison interval relative to the reference interval that is necessary for the comparison to be perceived as equal to the reference. The JND was calculated as half of the difference between the 75% and 25% points, and indicates the smallest detectable change in duration. The PSE is a measure of bias, while the JND reflects precision.

The goodness of fit was assessed with the Psignifit function "GoodnessOfFit", which returns a measure of the deviance of the data from the model and compares it against an empirical bootstrap distribution. A "good fit" was set as a further requirement for inclusion of the data in the analysis. The significance level of the test of "good fit" was set to .001, which corresponds to the value of .05 corrected with Bonferroni correction for 48 comparisons (24 participants, 2 conditions). We have chosen the conservative Bonferroni correction and adopted a strict further exclusion criterion, since we had already excluded during the course of the study all the participants unable to perform the task. Moreover, empirical bootstrap distributions were built out of small samples of 10 values; with small sample sizes, due to the limited variability in the sample, 95% confidence intervals contain the true parameter in less than 95% of the cases. The data can be found on the Open Science Framework (OSF) repository (http://osf.io/wm3cs).

The first part of the analysis examined whether the perceived change in duration was proportional to the magnitude of the reference interval: PSE and JND values expressed in milliseconds were entered separately into a one-way repeated-measures ANOVA with Reference (660, 462, and 330 ms) as the within-participant variable.

In the second part of the analysis, PSE and JND values expressed as percentages of the reference interval were entered into a two-way repeated-measures ANOVA with Auditory context (regular, non-regular) and Reference (660, 462, and 330 ms) as within-participant variables. PSE and JND were expressed as percentage of the reference interval, in order to average the values across reference intervals of different duration and compare the estimates between regular and non-regular auditory context.

In the third part, Bayesian analysis was applied to the non-significant comparisons of interest to our research question, in order to distinguish between evidence in favour of the null hypothesis from insensitive data (Dienes, 2014). A uniform distribution was chosen to represent the alternative hypothesis. The value chosen for the lower limit is standard and does not affect the results (Dienes, 2014), while the upper limit is set to the largest expected difference between the samples. Bayes factors for each comparison were obtained inserting the lower and the upper limits, the sample mean difference and the standard error of the difference in the online Bayes calculator provided by Zoltan Dienes (http://www.lifesci.sussex.ac.uk/home/Zoltan_Dienes/inference/bayes_factor.swf). Bayes factors < 1/3 and >3 were interpreted as evidence for the null and the alternative hypotheses, respectively (see Dienes, 2014).

4.5 Results

Four participants were excluded, because they did not meet the criterion set for the percentage correct (≥ 85%) for the two easiest conditions (S5: 72.5%; S6: 73.7%; S10: 83.7%; S18: 77.5%).

4.5.1 Duration discrimination across reference intervals – absolute measures

PSE. The effect of Reference was significant, $F_{(2, 46)} = 26.0$, $p = 3x10^{-8}$, $\eta_G^2 = 0.30$: the PSE values for the 660 ms reference (Mean [SD] = -23.8 [24.3] ms) were different from the values for the 462 ms (Mean [SD] = -1.52 [19.5] ms, $t_{(23)} = 6.19$, $p = 3x10^{-6}$, d = 1.26) and the 330 ms reference (Mean [SD] = 1.11 [10.8] ms, $t_{(23)} = 5.64$, $p = 10^{-5}$, d = 1.15); PSE values for the 462 ms and the 330 ms reference, instead, were comparable, $t_{(23)} = 0.80$, p = .43, d = 0.16. As shown in **Figure 4.3, panel A**, PSE values for the 660 ms reference were negative and farther from zero, compared to the other intervals, indicating that in the former case, comparisons shorter than 660 ms were systematically judged as longer then the reference.

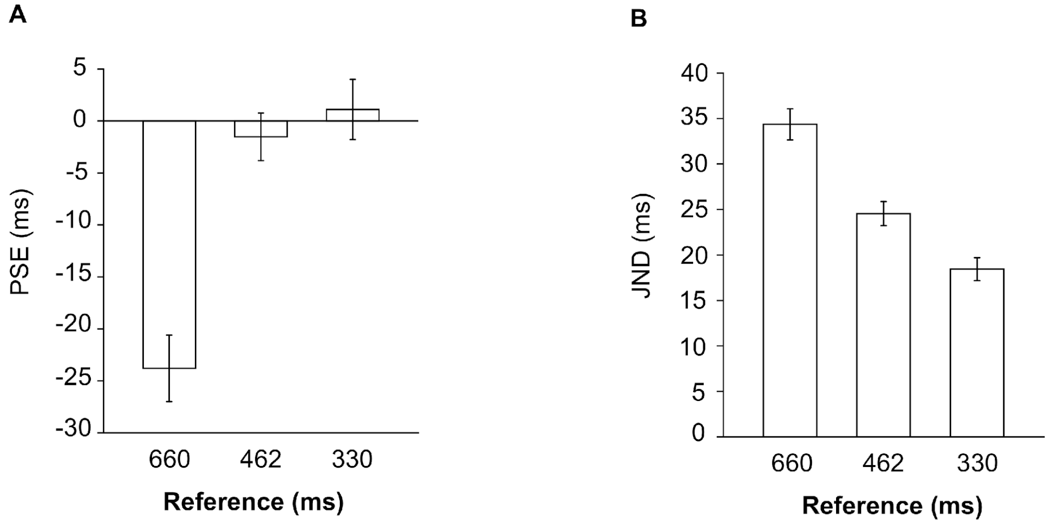


Figure 4.3 *PSE (A) and JND (B) values expressed in milliseconds, measured for each reference interval, averaging the values across regular and non-regular auditory context.*

JND. The effect of Reference was significant ($F_{(1.6, 36.7)} = 52.2$, $p = 2x10^{-10}$, $\eta_G^2 = 0.40$): smaller JND values were observed for the 330 ms reference (Mean [SD] = 18.4 [7.20] ms), compared to the 462 ms (Mean [SD] = 24.5 [9.04] ms, $t_{(23)} = 5.31$, $p = 2x10^{-5}$, d = 2.00) and the 660 ms reference (Mean [SD] = 34.4 [13.0] ms, $t_{(23)} = 9.81$, $p = 10^{-9}$, d = 1.49), as well as for the 462 ms (Mean [SD] = 24.5 [9.04]), compared to the 660 ms reference

(Mean [SD] = 34.4 [13.0] ms), $t_{(23)} = 5.27$, $p = 2x10^{-5}$, $d = 1.08$ (see **Figure 4.3, panel B**). This result indicates that duration discrimination was more precise for shorter than longer reference intervals. An estimate of the Weber fraction is given by the ratio of the JND observed for each reference to the duration of the reference. In accordance with the Weber-Fechner law (1860), the Weber fractions for the 660 ms (Mean [SD] = 0.052 [0.015]), the 462 ms (Mean [SD] = 0.053 [0.017]) and the 330 ms reference (Mean [SD] = 0.056 [0.018]) were comparable (all $t_{(23)} > 0.33$).

4.5.2 Influence of a regular context on duration discrimination – relative measures

PSE. The main effect of Reference was significant even when expressing the PSE as a percentage of increase/decrease in the length of the comparison relative to the reference ($F_{(2, 46)} = 16.6$, $p = 4x10^{-6}$, $\eta_G^2 = 0.18$): once again, PSE values observed for the 660 ms reference (Mean [SD] = -3.61 [3.68] %) were different from the PSE values for the 462 ms (Mean [SD] = -0.33 [4.23] %, $t_{(23)} = 5.03$, $p = 4x10^{-5}$, $d = 1.03$) and for the 330 ms reference (Mean [SD] = 0.34 [3.28] %, $t_{(23)} = 4.95$, $p = 5x10^{-5}$, $d = 1.01$), while the 462 ms and the 330 ms reference were comparable, $t_{(23)} = 0.90$, $p = .40$, $d = 0.18$. Neither the main effect of Auditory context, $F_{(1, 23)} = 3.26$, $p = .08$, $\eta_G^2 = 0.016$, nor the interaction between Reference and Auditory context, $F_{(2, 46)} = 2.37$, $p = .10$, $\eta_G^2 = 0.006$, passed the threshold for significance testing (see **Figure 4.4, panel A** and **Table 4.1**), indicating that the bias in duration discrimination, measured with different reference intervals was not significantly modulated by auditory context.

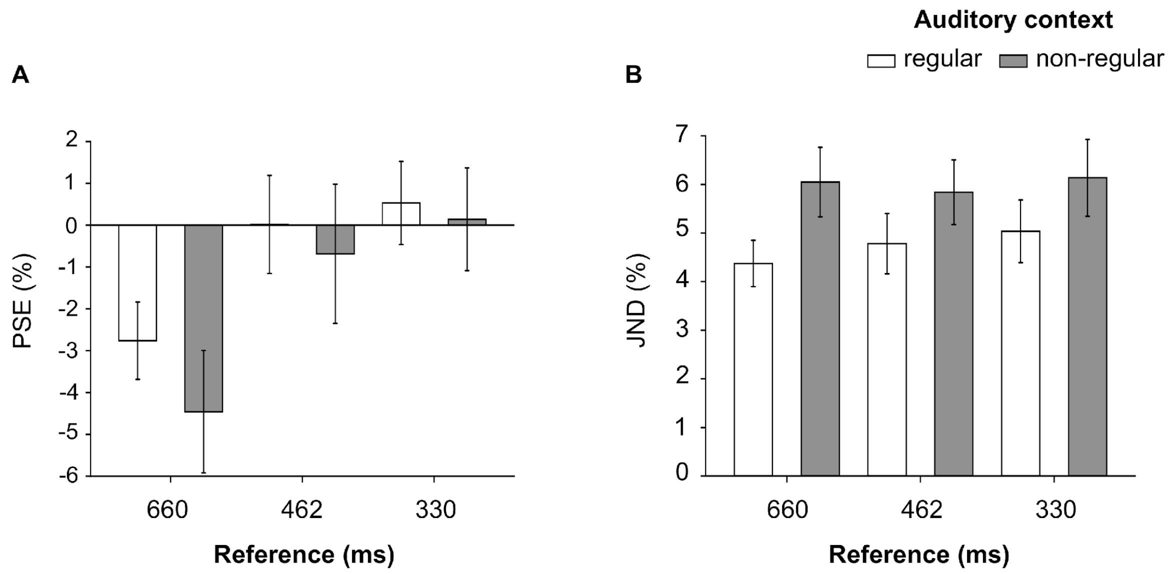


Figure 4.4 *PSE (a) and JND (b) values expressed as a percentage of increase/decrease in the length of the comparison relative to the reference interval (%), measured for the 660 ms, the 462 ms and the 330 ms reference intervals, with regular and non-regular auditory context.*

Table 4.1 *Means and (standard deviations) of PSE and JND values, expressed as a percentage of the reference interval, for each condition of experiment 4.1.*

	Auditory context	PSE (%)		JND (%)	
		Regular	Non-regular	Regular	Non-regular
Reference (ms)	660	-2.76 (2.73)	-4.46 (4.33)	4.37 (1.41)	6.05 (2.12)
	462	0.02 (3.47)	-0.68 (4.92)	4.78 (1.84)	5.84 (1.97)
	330	0.53 (2.94)	0.14 (3.63)	5.04 (1.91)	6.14 (2.34)

JND. The effect of Auditory context was significant ($F_{(1, 23)} = 28.8$, $p = 2x10^{-5}$, $\eta_G^2 = 0.10$), showing that overall the JND was smaller in the regular (Mean [SD] = 28.9 [9.31] %) compared to the non-regular condition (Mean [SD] = 39.8 [14.1] %). This result indicates that duration discrimination was more precise when a regular, compared to a non-regular context preceded the intervals to be discriminated. The interaction between Reference and Auditory context, instead, did not pass the threshold for significance testing ($F_{(2, 46)} = 0.74$, $p = 0.48$, $\eta_G^2 = 0.005$, see **Figure 4.4, panel B** and **Table 4.1**), indicating that the difference in precision with regular compared to non-regular context was comparable across reference intervals.

4.5.3 Distinguishing between no evidence and evidence for the null

Bayesian analysis was applied to the interaction between Auditory context and Reference, to examine whether the effect of regular context observed for the JND was comparable across reference intervals (evidence for the null). The lower bound was set to 0 %; the upper bound to 10.9 %, the mean difference between the regular and the non-regular condition observed in experiment 5.1. When we entered the values in the Bayes calculator we found evidence for the null, both when comparing the 660 ms and the 462 ms intervals (Mean [SE] = 0.68 [0.62] %, B = 0.22), the 660 ms and the 330 ms intervals (Mean [SE] = 0.71 [0.62] %, B = 0.25) and the 462 ms and the 330 ms intervals (Mean [SE] = -0.03 [0.41] %, B = 0.04). This result indicates that the difference in precision with regular compared to non-regular context was not modulated by the duration of the reference interval.

4.6 Discussion

When the values were expressed in milliseconds, duration discrimination for the 660 ms reference was more biased, compared to the 462 ms and the 330 ms intervals, since in the former condition the comparison interval was systematically judged as shorter than the 660 ms reference, while discrimination with the other intervals was more veridical (**Figure 4.3, panel A**).

Discrimination was also more precise for shorter compared to longer intervals, since smaller JND values were observed for the 330 ms reference, compared to all other intervals, and for the 462 ms compared to the 660 ms reference (**Figure 4.3, panel B**). This decrease in precision with longer intervals can be explained by the Weber-Fechner law (1860), which states that the JND between two physical magnitudes is proportional to the absolute magnitude. As a result of this, the ratio of the JND to the absolute magnitude is constant (Weber fraction). In accordance with the Weber-Fechner law, the Weber fractions estimated for the 660 ms, the 462 ms and the 330 ms reference intervals were similar. These results justify our choice of adapting the length of the comparison interval to the length of the reference, so as to fine-tune our method. Besides, expressing PSE and JND values as percentages of the reference interval allowed us to compare the influence of the auditory context across reference intervals.

When the values were expressed as relative measures, the discrimination bias for the 660 ms reference was still present, but was not modulated by the characteristics of the auditory context, since neither the main effect of Auditory context, nor the interaction between Reference and Auditory context passed the threshold for significance testing (**Figure 4.4, panel A**). Nevertheless, this bias could have been introduced by the auditory context, since both in the regular and non-regular conditions context intervals were close to 660 ms in duration. Since we have not come across a similar study reporting a similar perceptual bias, we have decided to refrain from speculation about this unexpected effect.

Duration discrimination, instead, was more precise with regular, compared to non-regular context, since smaller JND were observed when a regular context was presented. Contrary to expectations (i.e., Barnes and Jones, 2000), however, this effect of regular context was not modulated by the duration of the reference interval. The dynamic attending theory (DAT), instead, would predict better discrimination when the reference interval is equal in length to the intervals in the regular context, compared to shorter and longer intervals. In their study, Barnes and Jones (2000) observed that discrimination, measured as proportion correct, was best when the first interval to be discriminated lasted as long as the intervals in the regular auditory context, while it progressively decreased for longer and shorter intervals. Our data do not strongly support the dynamic attending theory, given that we found evidence for the null, when we compared the effect of context regularity observed for the JND across reference intervals.

Regarding the main effect of Auditory context observed for the JND, at least two factors can account for the difference in performance with regular and non-regular context: the easiness with which the beginning of the task can be anticipated, and the influence of a periodic auditory stimulation on attention. In experiment 4.1 we tried to make the reference interval unexpected, by presenting it after a variable number of low-frequency sounds, chosen at random between 3 and 5. Despite this attempt, the first high-pitched sound marking the reference interval in the regular, unlike in the non-regular condition, was always aligned with the low-pitched sounds in the context. The advantage observed with a regular context could therefore reflect the ability of participants to anticipate the task, rather than being the result of an entrainment between attention and the ongoing periodicity.

A second experiment was carried out with the intent to isolate the factors of anticipation and background regularity, and compare their individual contributions to interval discrimination against a condition in which both factors are at play. The objective of experiment 4.2 was to examine how likely each factor contributes to the effect of regular context observed in experiment 4.1.

4.7 Methods

4.7.1 Participants

Sixteen participants were recruited. Four were removed (see below), leaving a sample of 12 included in the study (mean ± SD age = 23.2 ± 3.3 years, 8 females). Participants provided written informed consent and participated in the experiment in return for payment (£7). All participants had normal hearing and no history of audiological or neurological disorder.

4.7.2 Stimuli

The stimuli of experiment 2 were similar to those used in experiment 1. The number of sounds in the auditory context varied between conditions and was either randomly selected between 3, 4, and 5, similarly as in Experiment 1, or it was equal to 1. When more than one low-frequency sound was presented, all sounds were regularly spaced, separated by a constant interval of 660 ms. The duration of the interval preceding the first high-pitched sound was either 660 ms, or cantered around 660 ms and were varied randomly by adding a normally-distributed amount of jitter N [0, 100] ms. The duration the reference interval was fixed at 660 ms.

4.7.3 Design

Figure 4.2, panel B illustrates the design of experiment 4.2. Auditory context is the single variable manipulated: the regular fixed context was a series of sounds randomly varying in number from 3 to 5, separated by blank intervals of 660 ms; the startle context was a single low-frequency sound, preceded and followed by blank intervals, the first varying in duration and the second fixed to 660 ms; the regular random context was the same as regular fixed, except for the fact that the duration of the interval preceding the first high-pitched sound was centred on 660 ms and varied randomly.

Despite the fact that the duration of the auditory context was comparable between conditions, the point in time when the reference was presented was not equally predictable. The reference could be easily anticipated in the startle condition, given that the first high-pitched sound always followed the single low-frequency sound by 660 ms. The regular fixed context was intermediate in terms of expectancy, as the first high-frequency sound was always aligned with the regular context, and was always presented after either 3, 4, or 5 low-frequency sounds. Regular random was the least predictable condition, despite being composed of regularly spaced sounds, because the length of the interval preceding the reference was varied randomly from trial to trial.

4.7.4 Procedure

Task and setting were the same as in experiment 4.1. Experiment 4.2 comprised three parts, one for each level of Auditory context (regular fixed, regular random, startle), run consecutively in a single session. Each part started with a practice block (20 trials) and was followed by two experimental blocks (2x50 trials). The order of the parts was counterbalanced.

4.8 Analysis

In the first part of the analysis, PSE and JND values were entered separately in a one-way repeated-measures ANOVA with Auditory context (regular fixed, regular random, startle) as within-participant variable.

In the second part, Bayesian analysis was applied in order to discriminate between insensitive data and evidence for the null. Similarly as in experiment 4.1, the alternative hypothesis was represented with a uniform distribution with the lower limit fixed to a standard and the upper limit set to the mean difference between the regular and non-regular conditions measured in experiment 4.1 for the 660 ms reference, which corresponds to the largest difference we expected to observe for the effect of Auditory context (**Table 4.2**).

Table 4.2 *Means and (standard deviations) for PSE and JND values, measured in experiment 4.1 and experiment 4.2 for the 660 ms reference interval, with different auditory context.*

Experiment	Auditory Context	PSE (ms)	JND (ms)
E 4.1	Regular	-18.2 (18.0)	28.9 (9.31)
E 4.1	Non-regular	-29.4 (28.6)	39.8 (14.1)
E 4.2	Regular fixed	-13.5 (24.2)	30.0 (11.8)
E 4.2	Regular random	-14.9 (29.2)	32.7 (12.2)
E 4.2	Startle	-12.2 (30.2)	33.6 (13.0)

4.9 Results

Four participants were excluded from the analysis: three participants were excluded because they did not meet the criterion set for percentage correct (≥ 85%) for the two easiest conditions (S3: 80.5%; S9: 73.7%; S13: 83.7%); one participant was excluded due to loss of data.

PSE. The main effect of Auditory context for PSE was non-significant ($F_{(1.1,\ 12.6)} = 0.034$, $p = 0.89$, $\eta_G^2=0.002$, **Figure 4.5, panel A**). Since a difference in bias with regular compared to non-regular context was not present in experiment 4.1, this effect was not examined further with Bayesian analysis. Similarly as in experiment 4.1, negative mean PSE values were observed for all the conditions.

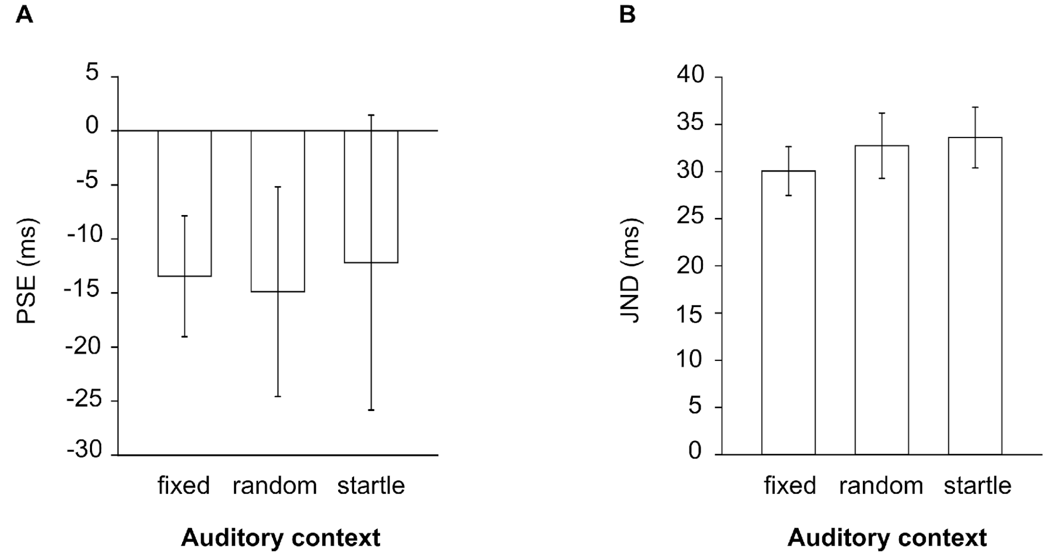


Figure 4.5 *PSE (A) and JND (B) values expressed in milliseconds, measured with regular fixed (fixed), random regular (random) and startle auditory context in experiment 2.*

JND. The main effect of Auditory context for JND was also non-significant ($F_{(2, 22)} = 0.68$, p = 0.52, η_G^2=0.016, **Figure 4.5, panel B**). When we applied Bayesian analysis (lower bound = 0 ms, upper bound = 10.8 ms) we found that the data was insensitive and did not support the null, both when comparing regular fixed with regular random (Mean [SE] = 2.68 [2.64] ms, B = 0.87), regular fixed with startle (Mean [SE] = 3.55 [2.42] ms, B = 1.56) and regular random with startle (Mean [SE] = 0.87 [2.39] ms, B = 0.46). The values observed for regular fixed, regular random and startle auditory context in experiment 2 were closer to the values measured with regular, compared to non-regular context in experiment 1 (**Table 4.2**).

4.10 Discussion

Duration discrimination both in terms of bias and precision, did not differ between regular fixed, regular random and startle auditory context. Given that the ANOVAs on the PSE and the JND values were not significant and that Bayesian analysis did not provide evidence in favour of the null, no conclusion can be drawn from this second study.

4.11 General Discussion

In our work, we examined whether a regular compared to a non-regular context can influence duration perception, measured with a 2-IFC perceptual judgment task. Our study was based on the work of Barnes and Jones (2000), who had previously shown that a regular context systematically influences the perceived duration of single auditory events, embedded in this context. In a series of seven experiments, these authors showed that listeners were more accurate in judging the duration of intervals that were equal in length to the intervals presented in the regular context, compared to shorter or longer intervals. In describing their results, the authors postulated that attention fluctuates over time and synchronizes with the ongoing auditory periodicity.

In our study, differently from Barnes and Jones (2000), we introduced a non-regular condition and used PSE and JND values to measure duration discrimination, instead of percentage correct. Our work aimed at measuring a general effect of regular compared to non-regular context; it also examined the effect of context regularity across reference intervals of different duration. Despite these differences, we expected to support the finding of Barnes and Jones (2000) by showing that duration discrimination with regular compared to non-regular context, was significantly better when the reference interval was the same as the context intervals (660 ms reference), compared to shorter intervals (462 and 330 ms). Even though temporal discrimination was more precise with regular compared to non-regular context, this effect was not selective for the duration of the reference interval. Bayesian analysis on the non-significant interaction between Reference and Auditory context in experiment 4.1 provided evidence for the null hypothesis and supported the conclusion that the effect of context regularity was not modulated by the duration of the reference interval. On a further note, duration discrimination for the 660 ms reference interval was also more biased, compared to all other intervals, but this effect was not modulated by the characteristics of the auditory context. Our speculation is that the divergence between our results and the results of Barnes and Jones (2000) stems from the methods used to quantify discrimination performance and from the range of reference intervals included in the experimental blocks.

Barnes and Jones (2000) assumed a constant linear relation between the perceived change in duration and the duration of the reference interval, and applied the Weber fraction to set the duration of the comparison interval. The comparison interval was expressed as a constant proportion of the reference interval and was either .12 (experiments from 1 to 6) or .09 (experiment 7). In our design the duration of the comparison interval was also proportional to the reference interval, but instead of being fixed, it varied among 5 magnitudes. Having a single magnitude for the comparison may not be ideal when comparing discrimination across reference intervals. Applying the Weber fraction, in fact, assumes a perfect linear relation between perceived change and magnitude of the stimulus; while a linear relation may hold for small magnitudes, a non-linear relation is more likely to apply to the discrimination of larger magnitudes (e.g., logarithmic, Weber-Fechner, 1860).

Furthermore, while Barnes and Jones presented trials with different reference intervals within the same block, we had a separate block for each reference (660, 462 and 330 ms). In three of the experiments reported (experiments 4, 5 and 6), Barnes and Jones (2000) included a no-context condition as a negative control. It is worth noting that even for the control condition they found an expectancy profile very similar to the one observed when a temporal auditory context preceded the temporal judgment. In their paper, the authors attributed this unexpected finding to the “session range effect” (p.283); explaining that judgments made about the interval duration are influenced by the range of values that occur in a block or session (Allan, 1979; Jamieson & Petrusic, 1975; Hellstrom, 1977, 1985; Woodrow, 1951). Since the expectancy profile found with auditory context was significantly greater than the profile found with no-context, Barnes and Jones attributed the expectancy profile to the influence exerted by contextual information on discrimination performance. In order to prove the robustness of the effect of context regularity, however, the results should be free from confounds: if the characteristic U-shaped expectancy profile results from presenting a regular auditory context prior to the discrimination, it should be observed independently of the range of values presented in each block or session.

Interestingly, this effect to some extent is compatible with what observed by Karl von Vierordt, summarised in the eponymous law (1868). According to Vierordt's law, long intervals tend to be judged as relatively shorter than they actually are, whereas short intervals are judged as longer. This effect was first observed with a time reproduction task, but was later replicated also with a duration discrimination task, among other estimation tasks (see Lejeune & Wearden, 2009).

More recently, studies have shown that perceptual judgment can be affected by the temporal context generated over the course of an experiment (Jazayeri & Shadlen, 2010; Cicchini et al., 2012). Jazayeri and Shadlen (2010) asked participants to reproduce the duration of intervals delimited by pairs of flashes, where these intervals were extracted from different probability distributions. The authors observed that participants tended to gravitate towards the mean of the distribution from which the intervals were extracted, overestimating the duration of shorter intervals and underestimating the duration of longer intervals. Cicchini, Arrighi, Cecchetti, Giusti and Burr (2012), however, showed that this *central tendency* effect, both in non-musicians and bowstring musicians, was less evident when the intervals were delimited by sounds, rather than by flashes, indicating that duration reproduction was more veridical in the auditory modality, compared to the visual modality. Furthermore, the authors did not observe a central tendency effect in drummers, which suggests that the influence of prior experience on perceptual judgment may be related to the degree of uncertainty in the response.

In a related line of study, Rhodes and Di Luca (2016) have shown that the perceived regularity of a sequence of sounds is influenced by the degree of regularity of the environment in which the sequence is embedded, thus suggesting that perception of temporal regularities is also affected by expectation.

On a final note, it is important to notice that the JDN was likely to be affected by the length of the auditory context, as discussed in the work of Sue, Rhodes and Di Luca (2016). In this work the authors constructed and compared several models that can account for how a perceptual system forms duration estimates. The Percept-Averaging model assumes that all intervals are stored in memory and are averaged by the perceptual system, to derive an estimate of the successive interval (Schulze, 1989; Sue et al., 2016). Similarly, the Multiple-Look Model assumes that the estimate measured with JND increases with the number of *looks* at each interval in a sequence (Drake & Botte, 1993; Sue et al., 2016). These two models require for the perceptual system to store in memory estimates of previous intervals and to calculate an average. A more parsimonious model, the Internal Reference (IR) model, computes an average iteratively, updating the estimate every time a new interval is presented (Sue et al., 2016). Despite procedural differences, all these models predicted an increase in discrimination performance as the number of intervals to be examined increased, a prediction that is consistent with the behavioural results (Sue et al., 2016).

4.12 Conclusions

In our work we re-examined the effect of a regular auditory context on duration discrimination, previously shown by Barnes and Jones (2000) and part of the dynamic attending theory (DAT). According to DAT, duration discrimination benefits maximally from a regular context when the reference interval, the first interval to be discriminated, is equal in duration to the intervals in the context. Discrimination of intervals shorter or longer than the context interval, instead, progressively decreases.

With our experiments we showed that duration discrimination of two intervals presented in a sequence can be influenced by an auditory context, since discrimination in experiment 1 was more precise when reference and comparison intervals were preceded by a regular compared to a non-regular context. Contrary to what we expected in view of Barnes and Jones (2000), however, this difference in discrimination with regular compared to non-regular context did not depend on the relationship among the intervals in the context and the first interval to be estimated. Not only was discrimination with regular compared to non-regular context not selective for the duration of the reference interval, but discrimination for the 660 ms reference interval was also more biased compared to the 462 ms and 330 ms intervals, both with PSE values expressed in absolute and in relative measures. According to our understanding, the discrepancy between our results and the results of Barnes and Jones (2000) is likely to be due to the differences in the methods and measurements used to quantify discrimination performance and to the presence of the *session range* effect, likely a confounder, in Barnes and Jones (2000).

To conclude, the work carried out supports an alternative interpretation for the U-profile reported by Barnes and Jones (2000), which forms the basis of the Dynamic Attending Theory (DAT): the authors explained this effect as the entrainment of attentional resources to external periodicities, however, this effect may be at least in part explained by non-attentional, decisional factors, as described by the central tendency (or session range) effect.

Chapter 5. Role of the cerebellum in intermittent and continuous auditory-motor synchronization: A single-pulse TMS study.

5.1 Abstract

The cerebellum has been proposed to play a role in timing, both in temporal perceptual judgments and in the execution of timed actions. As reported in a clinical study, when tapping along with a rhythmic auditory stimulus, patients with cerebellar ataxia showed greater tapping variability, measured as a coefficient of variation of the times between consecutive taps, as compared to healthy controls. Increased tapping variability was observed in intermittent tapping, when patients had to insert a pause within each cycle, but not when executing continuous movements. Even though the increased variability might simply be due to a difficulty in initiating and interrupting finger movements, reflecting reduced motor control, it has previously been attributed to impaired timing processes. With the aim to examine whether the variability observed in intermittent movements is associated with impaired motor control, single-pulse transracial magnetic stimulation (sTMS) – a method of interfering directly with brain function – was employed. Healthy adults were asked to tap in synchrony with a beat, executing continuous and intermittent movements. On each trial, single TMS pulses were delivered over the left or right cerebellar hemispheres, either during the upward or the downward phase of the movement, at the point in time when the finger started to decelerate. The critical condition involved stimulating the cerebellar hemisphere ipsilateral to the moving hand, when participants were tapping intermittently: finger tapping variability measured in this condition was expected to be significantly higher compared to the variability measured in continuous tapping, when stimulating the contralateral hemisphere. Given that each cerebellar hemisphere is connected to the ipsilateral side of the body, TMS was expected to increase tapping variability when stimulating the ispilateral compared to the contralateral hemisphere. In experiments reported, TMS had an effect on finger-tapping, but the effect was short-lasting and was not hemispheric-specific. This effect most likely resulted from the discomfort or the non-habituating startle-like reflex induced by TMS, rather than from a direct interference of the stimulation with cerbellar function.

5.2 Introduction

When tapping along with a rhythmic auditory stimulus in a synchronise-continue task, patients with cerebellar ataxia, a neurological condition characterized by abnormal motor control, originating from an alteration of the cerebellar system, showed a larger tapping variability, measured as a coefficient of variation of the times between taps, as compared to healthy controls (Spencer et al., 2003). Increased tapping variability was observed in intermittent tapping, when patients had to insert a pause within each cycle, whether tapping against a surface (e.g., a touch pad) or drawing circles in the air. When cerebellar patients were asked, instead, to produce continuous movements, either drawing circles or tapping in the air, their finger-tapping variability did not differ significantly from healthy controls. This dissociation between intermittent and continuous movements does not seem to depend on the complexity of the movements executed, as it has been observed both in finger-tapping and circle drawing, despite the fact that circle drawing requires control of multiple joints, while finger-tapping involves movements of a single joint (Spencer et al., 2003).

Spencer and colleagues (2003) explained this difference in variability by positing that in intermittent, unlike in continuous movements, “temporal control is achieved by the setting of explicit temporal goals” (p. 1438, “event timing”, timing account), while the temporal dynamics of continuous movements are “emergent” and result from the setting of non-temporal movement parameters, such as speed or acceleration (“emergent timing”). The authors concluded that the cerebellum is essential for the representation of temporal goals. In support of a role of the cerebellum in temporal processing, duration judgement of auditory events was shown to be impaired in patients with cerebellar ataxia compared to healthy controls (Grube et al., 2010). An alternative explanation of the increased tapping variability, later taken into account by Spencer, Ivry, and Zelaznik (2005), attributes the dissociation between intermittent and continuous movements to a difficulty in the transition between the onset and offset when initiating or interrupting a movement, as a result of a motor deficit. It is interesting to note, in fact, that increases in the variability of tapping or circle drawing in unilateral cerebellar patients with cerebellar ataxia was limited to the limb ipsilateral to the lesion (Spencer et al., 2003; Ivry et al., 2002).

Examining the characteristics of intermittent and continuous rhythmic movements in healthy individuals will facilitate the interpretation of the increase in tapping variability observed in patients with cerebellar ataxia in intermittent, but not continuous tapping. In the present work, TMS has been used in an attempt to provide convergent evidence with the lesion studies (i.e., Spencer et al., 2003).

TMS has been used before, to examine the casual role of the cerebellum in perceptual timing (Theoret et al., 2001; Fierro et al., 2007; Kock et al., 2007; Lee et al., 2007; Grube et al., 2010). Del Olmo and colleagues (2007) used repetitive TMS over the cerebellum to interfere with finger-tapping synchronization with visual and auditory stimuli and finger-tapping continuation without a pacing stimulus. The authors reported that rTMS increased finger-tapping variability for synchronization in the auditory modality, but not for synchronization in the visual modality or continuation. This effect was also hemispheric-specific, since it was larger for TMS over the right, compared to the left cerebellar hemisphere.

In the present study I used single-pulse TMS to interfere directly with continuous and intermittent paced tapping in healthy adult participants. The aim was to examine whether TMS over the cerebellar hemisphere ipsilateral to the moving hand, increased finger-tapping variability, compared to TMS over the analogous contralateral region. Healthy adults were asked to tap in synchrony with a beat and executed 32 intermittent or continuous oscillatory movements in the air. During each trial, single TMS pulses were delivered over the left or the right cerebellar hemispheres, either during wrist flexion or extension. Magnetic stimulation was triggered online, based on movement kinematics. The critical condition involved stimulating the cerebellar hemisphere ipsilateral to the moving hand, when participants were tapping intermittently: In accordance with Del Olmo (2007), finger-tapping variability measured in this condition was expected to be significantly higher compared to the variability measured in continuous tapping, when stimulating the contralateral hemisphere. Given that each cerebellar hemisphere is involved in movements of the ipsilateral side of the body, an increase in tapping variability when stimulating the ipsilateral compared to the contralateral hemisphere in intermittent compared to continuous tapping would provide converging evidence with the lesion studies.

5.3 Methods

5.3.1 Participants

Eight participants were recruited. Two were excluded, one for bad head-coil fit and one for unmet inclusion criteria, leaving a sample of six (6 females, 6 right-handed, M ± SD age = 21.5 ± 2.4 years). All participants provided written informed consent and took part in the experiment in return for payment (£30). All participants had normal hearing and no history of audiological or neurological disorder. The study was approved by the research ethics committee (SoPEC 990) of the University of Nottingham and was conducted in accordance with the Declaration of Helsinki (as of 2008).

5.3.2 Magnetic stimulation

Magnetic stimulation was performed by a Magstim 200^2 (BiStim) magnetic stimulator with a 130 mm double-cone coil. Single-pulse TMS was applied over the left or right lateral cerebellar hemispheres. The target sites were 1 cm below and 3 cm lateral to the inion. These sites were chosen to minimize the distance between the scalp and the deep cerebellar tissue, thus increasing the likelihood of effectively stimulating the target region (Hardwick et al., 2014). The coil was positioned tangentially to the scalp, at a 45° angle relative to the axial plane and with the handle pointing backward. When applying TMS we ensured that the coil made contact with the scalp and overlaid the target site, as much as allowed by the coil-head fit. The mean [SD] head size was 33.4 [1.1] cm from nasion to inion and 35.7 [1.3] cm from left to right pre-auricular points. Stimulation intensity for the experiment was set to 5-10% of maximum stimulator output (MSO) below the approximate threshold for brainstem stimulation, a mean [SE] of 59.2 [2.0] % of MSO. This threshold was chosen based on an estimate of the resting motor threshold (RMT) for stimulating the brainstem and evoking MEPs (> 50 µV in at least 10 of 20 trials, Rossini et al., 2014) in ipsilateral muscles. Brainstem evoked MEPs, however, were identified only in 2/6 participants. When a clear motor evoked response was not observed, stimulation intensity for the experiment was set to the highest intensity that was tolerable to the participant. When delivering sham stimulation (no-TMS condition) the coil was attached to a retractable arm placed above the participant’s head.

5.3.3 Auditory stimuli

Auditory stimuli were series of 32 sounds of 50 ms duration, gated on and off with a 10 ms linear ramp. The sounds had frequency of 660 Hz and were interspersed with blank intervals of 700 ms. All sounds were built in LabView and played from the PC built-in sound card at a fixed intensity that was comfortable to the participant.

5.3.4 Procedure

Participants were instructed on the task and gave their written consent to the study. They were seated on a swivel chair. Two pairs of electrodes were attached over their right flexor digitorum superficialis (FDS) and extensor digitorum communis (EDC) muscles, after abrading the skin to increase electrical conductance. Motion trackers were attached to the tip of the right index finger and to the right elbow. Participants were asked to wear earplugs in order to protect their ears from the loud click produced by the stimulator as the unit's capacitor is discharged. At the beginning of the experiment, a threshold for the intensity of stimulation was estimated in order to set the intensity of stimulation for the experiment. During the experiment participants were asked to keep their forearm flexed, with their elbow resting on the arm-chair and their right hand lifted up. Each trial began with a computer check of the elbow's position. When the elbow's detected position was within 5 cm from the recorded starting position, a high-pitched sound (1000 Hz, 150 ms) was presented to signal the start of the trial. Each trial was a sequence of 32 regularly spaced sounds, starting 1.5 s after the start signal. On each trial, participants listened to the sequence of sounds, and were required to tap in synchrony with the beat, reaching full wrist flexion on the beat and full wrist extension on the offbeat. Participants were instructed to execute vertical oscillatory movements with their wrist, while keeping their index finger straight. The experiment comprised two sessions of approximately 90 minutes each. Depending on the session, participants were required to execute continuous or intermittent movements. In both versions of the task, participants tapped in the air without contact with a surface. In intermittent tapping, participants were instructed to interrupt the movement at each cycle, at the peak of wrist extension, while in continuous tapping they were asked to keep the movements smooth and uninterrupted. The sessions were run on separate days, (mean [SD] = 1.4 [0.5] days in between). The order of the sessions was counterbalanced: half of the participants started with intermittent tapping, half with continuous tapping. Each session included 6 blocks of 12 trials each. On each trial, single

TMS pulses were delivered at random every 4, 5 or 6 cycles of 750 ms, every 3.75 s on average. A mean [SD] of 5.70 [0.16] TMS pulses per trial was delivered for each condition. In each block, TMS was triggered at wrist extension in half of the trials, and at wrist flexion in the remaining half. The order of the trials within each block was randomized. In the first and the fourth block participants did not receive TMS and the coil was attached to a retractable arm placed above the participant's head. In these no-TMS blocks magnetic pulses were triggered with the same algorithm used in the TMS blocks, so that the loud noise produced by the stimulator could be heard in the background. In the four remaining blocks, TMS was applied either over the left or over the right cerebellar hemisphere (lCB and rCB). The order of these blocks was counterbalanced (i.e., lCB-rCB-rCB-lCB or rCB-lCB-lCB-rCB).

5.3.5 Online TMS triggering

The position of the index finger was processed online and used to trigger the TMS pulses. First, velocity and acceleration along the vertical axis were derived from position. Acceleration was then filtered with a digital point-by-point second-order Butterworth low-pass filter (Butterworth Filter PtByPt VI, LabView) with cutoff frequency of 4 Hz, in order to remove all frequency components > 4 Hz, which were unrelated to the task. A value of 4 Hz was chosen based on empirical testing. Notice that the expected tapping cycle was 750 ms, which corresponds to a frequency component of 1.33 Hz for position, and to a 4 Hz component for acceleration. Velocity and online filtered acceleration were used to detect the point in time during wrist extension, when the finger started to decelerate. A deceleration was detected at zero-crossing of filtered acceleration, with the additional criterion of velocity along the vertical axis ≥ 15 cm/s. TMS was triggered after a random delay selected from a uniform distribution in the range [0, 100] ms from the point detected, aiming to trigger a single TMS pulse at wrist extension. In order to stimulate at wrist flexion, the point detected was further delayed by half a cycle (325 ms). The decision to use the point detected at extension to deliver the TMS pulse at flexion was based on pilot testing: a higher wrist velocity was measured for the downward phase (mean [SD] = 40.6 [9.4] cm/s), compared to the upward phase (mean [SD] = 34.5 [5.8] cm/s) of a tapping cycle; as a result of this, the point detected at flexion tended to be closer than 100 ms to the tap and the TMS pulse would undesirably be delivered during the following extension phase.

5.3.6 Apparatus

The LabChart software was used to sample the digital trigger for each TMS pulse delivered, the start of sampling of motion tracking at the beginning of each trial and the auditory stimuli presented. The delay measured between the start of sampling of motion tracking and the start of the auditory presentation was used to realign in time the two recordings. A custom python script was used for pre-processing of all data. The machine learning python library scikit-learn was used for classification analysis. The free software R (R Core Team, 2016) was used for statistical testing.

5.4 Analysis

The position of the index finger was preprocessed as explained in **Chapter 3**, **Section 3.4.1**. First, intermittent and continuous tapping were compared, with the aim to check whether the kinematics recorded in these conditions differed as expected and to ensure that participants executed the task correctly. Secondly, auditory-motor synchronization performance was assessed, first examining whether TMS had a local effect on the taps around the time of stimulation, as well as a global effect over the whole trial on auditory-motor synchronization performance. In the end median cycle velocity was examined as a possible confound.

5.4.1 Intermittent and continuous tapping

Intermittent and continuous tapping were examined by looking at the duration of the pause up, at full wrist extension, and at the degree of asymmetry in the duration of the pauses up and down (at full flexion). Given that in intermittent tapping participants were instructed to insert a pause at full extension, in intermittent compared to continuous tapping we expected to measure a longer pause up and a larger pause asymmetry. The pauses were defined as the longest continuous intervals with velocity < 3.5 cm/s. The duration of the longest pause up and down were calculated for each tapping cycle and averaged within trials. The proportion of pause asymmetry was calculated by taking the difference, divided by the sum of the two pauses at every tapping cycle, then averaging within trials.

In order to explore the differences between continuous and intermittent finger-tapping across participants and to ensure that all participants executed the task correctly, I applied classification analysis on the two features extracted, the duration of the pause up and pause asymmetry. Having a two-dimensional set facilitated the comparison across participants and allowed for better understanding of the data, compared to higher-dimensional sets. A good separation between continuous and intermittent tapping based on the movement kinematics, in fact, does not guarantee that participants were tapping in an intermittent and continuous manner. Each feature was normalized within subjects by subtracting the mean and dividing by the standard deviation, in order to prevent features with larger values having a stronger impact on the classification. The models were trained on 2/3 of the data, leaving out 1/3 of the data for testing. Training and testing were repeated 3 times, each time leaving out a different set for testing, according to a 3-fold cross validation procedure. Cross validation was applied in order to limit the problem of overfitting. Classification performance was quantified as the area under the receiver operating characteristic (AUCROC) curve (function sklearn.metrics.roc_auc_score), measured from the binary observed and predicted values at testing. The area under the curve was chosen as a measure of classification performance, because it deals with an uneven number of instances for the two classes in the dataset. The AUCROC score was used to decide whether participants executed the task correctly: participants with average AUCROC at test < 0.60 (i.e., the set classification threshold) were excluded from the study. Two different machine-learning algorithms were used, to examine whether the results of the classification were affected by the model selected: 1) logistic regression (sklearn.linear_model.LogisticRegression); 2) linear support vector machine (SVM, sklearn.linear_model.LogisticRegression, kernel='linear'). The model parameter "C" was set to e^{20} in order to render inefficient the parameter regularization applied by default by Scikit-learn. The AUCROC values for each classification model (logistic regression, linear SVM) were entered in a two-tailed paired Welch's t-tests for statistical testing. After excluding from the analysis those participants who did not execute the task correctly (see below), the values of pause duration were averaged within blocks and entered into an ANOVA (3x2x2x2) with TMS (noTMS, lCB, rCB), Tapping (continuous, intermittent), TMS time (flexion, extension), and pause (up, down) as within-participant variables.

5.4.2 Local effect of TMS

This part of the analysis is a zoom-in on the taps around the time of TMS. Given that consecutive TMS pulses were separated by an average of 4.55 ± 0.05 ITI, I considered 4 intervals around the time of TMS, from one tap preceding a TMS pulse up to the two taps following a pulse (i.e., –1, 0, 1, 2), to examine the local effect of TMS on finger-tapping. All TMS pulses that were not followed by at least two taps were excluded from this analysis (6.42%). All TMS pulses that were not followed within 2/3 of a cycle by a pause when stimulating at extension, and by a tap when stimulating at flexion, were also discarded (2.72%). The ITI were averaged within trials and blocks and entered into a repeated-measures ANOVA with TMS (no-TMS, lCB, rCB), Tapping (continuous, intermittent), TMS time (flexion, extension), and ITI to TMS (–1, 0, 1, 2) as within-participant variables.

5.4.3 Global effect of TMS

The mean inter-tap-interval (mean ITI), the coefficient of variation of ITI (CoV ITI) and the mean negative asynchronies (mean NA) calculated over the whole trial, were compared across conditions, in order to estimate the impact of cerebellar TMS over the whole trial. The aim of this analysis was to examine whether cerebellar TMS is associated with an increase in tapping variability, measured with the coefficient of variation. The mean tapping rate, measured with mean ITI, and the mean (negative) asynchronies were analysed for completeness. All values were averaged within blocks and entered separately into a repeated-measures ANOVA with TMS (noTMS, lCB, rCB), Tapping (intermittent, continuous) and TMS time (flexion, extension) as within-participant factors.

5.5 Results

The results are divided into three main sections. The first section (i.e., **5.5.1**) includes the results on the distinction between intermittent and continuous tapping. The tests reported in this section were run to show that intermittent and continuous tapping could be correctly classified, based on parameters extracted from their movement kinematics.

The second section (i.e., **5.5.2**) includes the results for an effect of TMS on the taps around the time of stimulation. This analysis was exploratory and was run to characterise any short-lasting effect of TMS.

The third section (i.e., **5.5.3**) includes the results for the tests of the main hypothesis of a global effect of TMS on finger-tapping variability, measured with coefficient of variation (CoV) of ITI calculated over an entire trial. More specifically, when TMS was delivered over the right, compared to the left cerebellar hemisphere, I expected to observe an increase in CoV ITI. In this section, mean ITI and mean NA were also examined to have a full picture of the global effect of TMS on finger tapping performance.

5.5.1 Intermittent and continuous tapping

Classification performance with logistic regression and linear SVM was comparable ($t_{(6)} = 1.12$, $p = .30$, $d = 0.086$). All participants had AUCROC > .65, except for S6, who was excluded from the analysis (see **Figure 5.1** for an example).

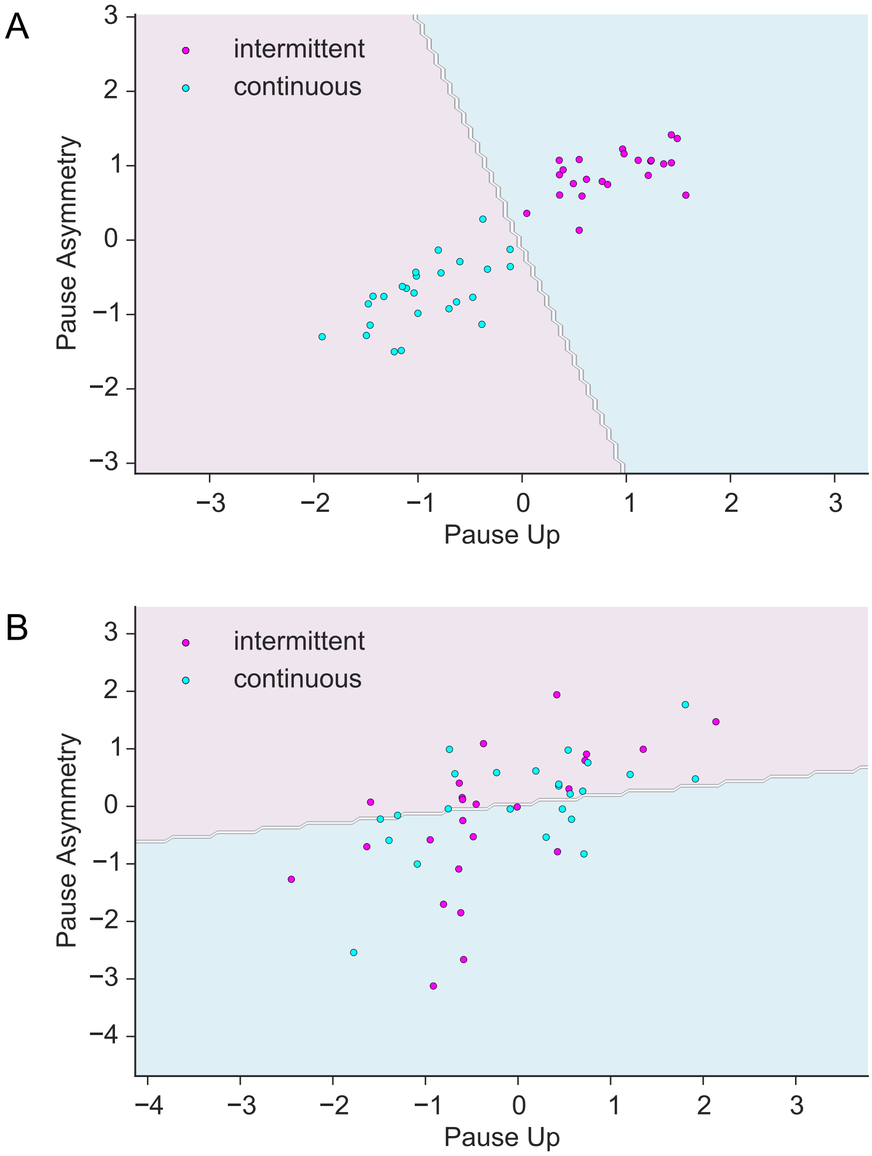


Figure 5.1 *Example for test data and decision boundaries obtained with logistic regression, separating intermittent tapping (magenta) from continuous tapping (cyan) for one participant included (A) and the only participant excluded from the analysis (B).*

On average the pauses up, mean [SD] = 273 [46.8] ms, lasted longer than the pauses down, mean [SD] = 57.2 [54.1] ms ($F_{(1,5)} = 48.4$, $p = .0009$, $\eta_G^2 = 0.8$). The duration of the pauses up tended to be longer in intermittent tapping (mean [SD] = 295 [38.1] ms) compared to continuous tapping (mean [SD] = 250 [43.8] ms, $F_{(1,5)} = 5.42$, $p = .067$, $\eta_G^2 = 0.1$).

5.5.2 Local effect of TMS

When the mean ITI from one tap preceding up to the two taps following a TMS pulse were analysed with an ANOVA (3x2x2x4) with TMS (no-TMS, lCB, rCB), Tapping (intermittent, continuous), TMS time (flexion, extension), and ITI to TMS (–1, 0, 1, 2) as within-participant variables, the effects that passed the threshold for significance were the third order interactions between TMS, Tapping and TMS time ($F_{(1.7,8.4)} = 11.46$, $p = .005$, $\eta_G^2 = 0.05$) and the fourth order interaction between all the variables ($F_{(6,30)} = 2.42$, $p = .05$, $\eta_G^2 = 0.03$), while the third order interaction between TMS, Tapping and ITI to TMS after GG correction approached significance ($F_{(2.1,10.7)} = 3.40$, $p = .067$, $\eta_G^2 = 0.03$). Given that the previous analysis on ITI variability had shown a significant interaction between TMS and Tapping, and that the comparison between TMS at extension and at flexion is not central to the study, we decided to run separate analysis on the data for TMS at wrist extension and flexion. The ITI were re-entered separately for TMS time in an ANOVA (3x2x4), with TMS (no-TMS, lCB, rCB), Tapping (intermittent, continuous) and ITI to TMS (–1, 0, 1, 2) as within-participant variables. When TMS was delivered at wrist flexion, the main effect of TMS passed the alpha threshold ($F_{(2,5)} = 4.78$, $p = .035$, $\eta_G^2 = 0.04$), together with the interaction between TMS and ITI to TMS ($F_{(6,30)} = 2.42$, $p = .05$, $\eta_G^2 = 0.07$): the mean of ITIs measured at lag-1 from the TMS pulse was shorter when TMS was applied over the right hemisphere (mean [SD] = 731 [13.6] ms) compared to when TMS was not applied (mean [SD] = 745 [4.76] ms, $t_{(5)} = 3.01$, $p = .03$, $d = 1.23$). The mean ITI at lag-1 with TMS over the right (mean [SD] = 731 [13.6] ms) also tended to be shorter, compared to the left hemisphere (mean [SD] = 741 [16.3] ms, $t_{(5)} = 2.06$, $p = .09$, $d = 0.84$, see **Figure 5.2**).

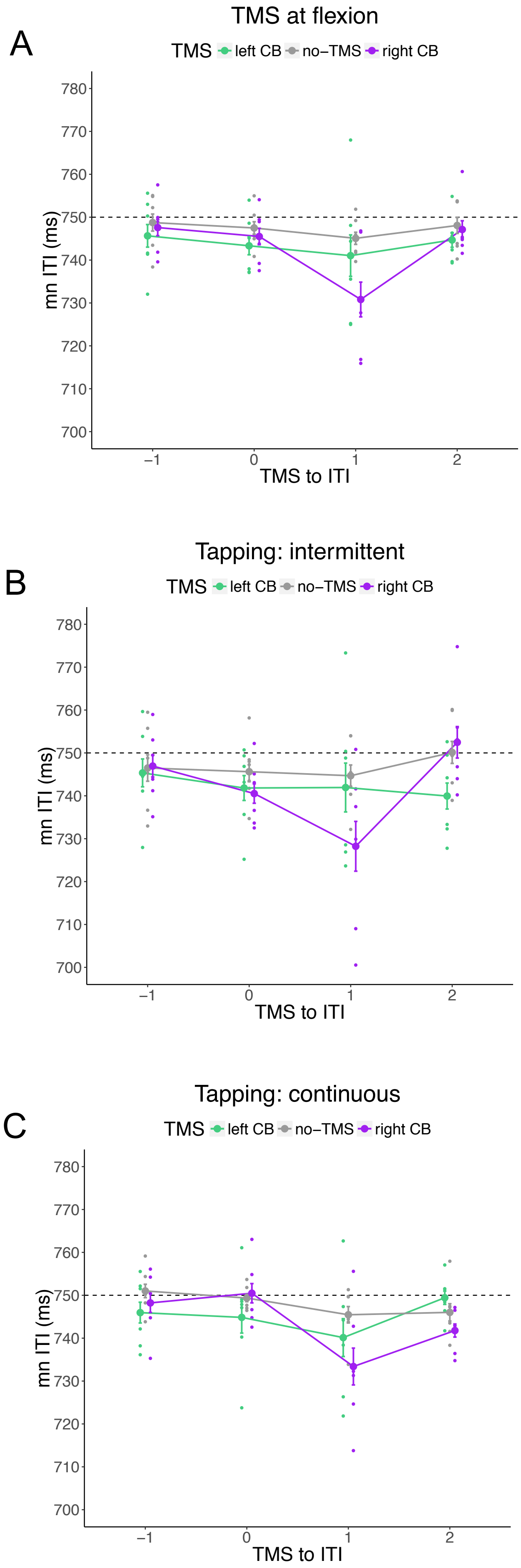


Figure 5.2 *Mean ITI from one inter tap interval (ITI) preceding (–1 on x-axis) up to two ITI following a TMS pulse (0, 1, 2 on x-axis), when TMS was delivered at wrist flexion: difference across TMS conditions (A) and separately for intermittent tapping (B) and continuous tapping (C). Error bars are 95% between-participants confidence intervals.*

When TMS was delivered at wrist extension, with the finger moving upward and before the pause, the effect of TMS on mean ITI differed between continuous and intermittent tapping (interaction between Tapping and ITI to TMS: $F_{(3,15)} = 17.8$, $p = .00003$, $\eta_G^2 = 0.1$): at lag 0 from the TMS pulse mean ITI was higher for intermittent compared to continuous tapping ($t_{(5)} = 4.61$, $p = .006$, $d = 0.78$), this difference reversed, with lower mean ITI for intermittent compared to continuous tapping at lag 1 ($t_{(5)} = 2.75$, $p = .04$, $d = 1.10$) and lag 2 ($t_{(5)} = 3.49$, $p = .02$, $d = 1.43$). In intermittent tapping, at lags ≥ 1 the mean was farther away from the 750 ms target interval compared to continuous tapping (see **Figure 5.3, panel A**).

These differences between intermittent and continuous tapping were more pronounced when TMS was applied on the head than when the pulses were sent in the air (interaction between TMS, Tapping and ITI to TMS: $F_{(6,30)} = 3.61$, $p = .008$, $\eta_G^2 = 0.07$). The post-hoc comparisons showed a significant difference in intermittent tapping between TMS over the left CB and no-TMS at lag 1, $t_{(5)} = 2.91$, $p = .03$, $d = 1.19$, and lag 2, $t_{(5)} = 6.78$, $p = .001$, $d = 2.77$, and between TMS over the right CB and no-TMS at lag 2 ($t_{(5)} = 4.21$, $p = .008$, $d = 1.72$); in continuous tapping between TMS over the left CB and no-TMS at lag 2, $t_{(5)} = 3.54$, $p = .016$, $d = 1.45$ (see **Figure 5.3, panel B and C**).

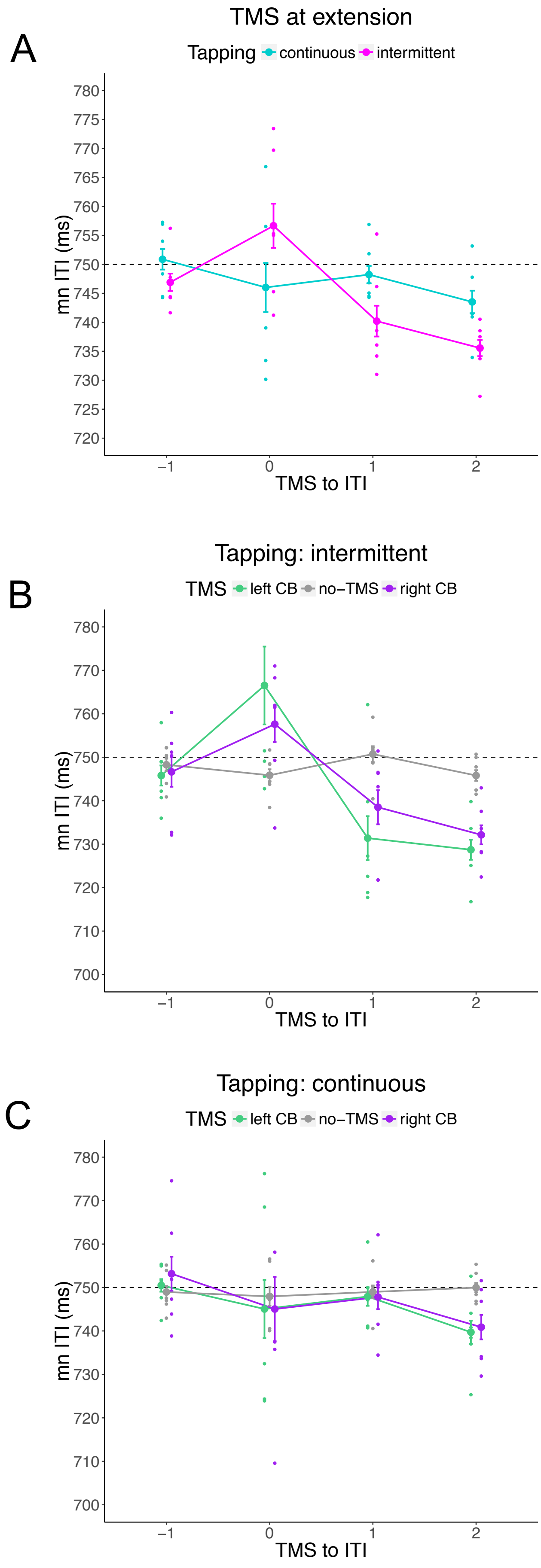


Figure 5.3 *Mean ITI from one inter tap interval (ITI) preceding (–1 on x-axis) up to two ITI following a TMS pulse (0, 1, 2 on x-axis), when TMS delivered at wrist extension: difference between continuous and intermittent taping (A); pattern of results observed for intermittent tapping (B) and continuous tapping (C) compared across TMS conditions. Error bars are 95% between-participants confidence intervals.*

5.5.3 Global effect of TMS

5.5.3.1 Inter-tap-interval (ITI)

The mean ITI differed across TMS conditions (main effect of TMS: $F_{(1.5,7.6)} = 5.82$, $p = .03$, $\eta_G^2 = 0.1$). The mean ITIs were shorter and farther away from the 750 ms target interval when TMS was applied over the left cerebellar hemisphere (mean [SD] = 741 [5.3] ms, $t_{(5)} = 2.61$, $p = .048$, $d = 1.07$) and over the right cerebellar hemisphere (mean [SD] = 741 [5.0] ms, $t_{(5)} = 2.62$, $p = .047$, $d = 1.07$) compared to when TMS was not applied (mean [SD] = 745 [3.1] ms), while mean ITI with TMS over the left and right hemisphere was comparable, $t_{(5)} = 0.45$, $p = .67$, $d = 0.18$. These differences in the mean ITI across conditions were unexpected, since finger-tapping was paced by an external auditory stimulus, and were explained by the fact that the number of taps per trial differed across TMS conditions (main effect of TMS: $F_{(2,10)} = 9.86$, $p = .0043$, $\eta_G^2 = 0.2$). Participants executed more taps per trial when TMS was delivered over the left cerebellar hemisphere (mean [SD] = 32.7 [0.4], $t_{(5)} = 2.72$, $p = .042$, $d = 1.11$) or over the right cerebellar hemisphere (mean [SD] = 32.7 [0.3], $t_{(5)} = 4.17$, $p = .0087$, $d = 1.70$) compared to when TMS pulses were sent in the air (mean [SD] = 32.3 [0.2]).

5.5.3.2 Coefficient of variation of ITI

TMS affected also finger-tapping variability, measured with the coefficient of variation of ITI (Interaction TMS-Tapping: $F_{(2,10)} = 4.32$, $p = .044$, $\eta_G^2 = 0.04$). When TMS was applied over the left cerebellar hemisphere, tapping variability was higher in intermittent (mean [SD] = 6.02 [1.28]%) compared to continuous tapping (mean [SD] = 5.39 [0.75] %, $t_{(5)} = 2.55$, $p = .051$, $d = 1.04$). When TMS was not applied, instead, intermittent tapping tended to be less variable than continuous tapping ($t_{(5)} = 1.13$, $p = .31$, $d = 0.46$). As a result of this, in intermittent tapping the coefficient of variation was higher when TMS was applied over the left hemisphere (mean ± SD = 6.02 ± 1.28 %) compared to when it was not delivered (mean [SD] = 4.99 [0.79] %, $t_{(5)} = 2.33$, $p = .067$, $d = 0.95$), while it did not differ between TMS over the left and the right hemispheres, $t_{(5)} = 1.44$ $p = .21$, $d = 0.60$ (**Figure 5.4**).

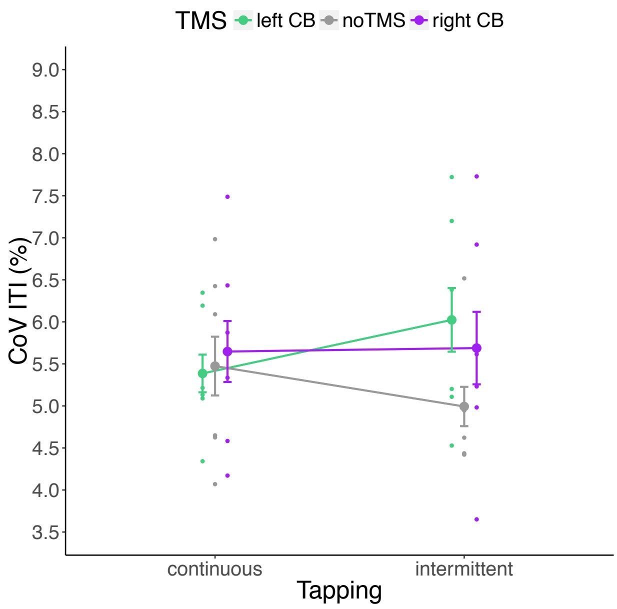


Figure 5.4 *Coefficient of variation of ITI (%) for intermittent and continuous tapping, when TMS was applied over the right CB (purple) and the left CB (green) and when TMS was not delivered (grey). Error bars are 95% between-participants confidence intervals.*

5.5.3.3 Negative asynchronies (NAs)

TMS affected also the negative asynchronies ($F_{(1.8,9.1)} = 46.72$, $p = .00002$, $\eta_G^2 = 0.4$): the time mismatch between taps and sounds was larger in the TMS compared to the no-TMS conditions, and participants tapped earlier with respect to the sounds when TMS was applied over the left hemisphere (mean [SD] = –86.2 [32.3] ms, $t_{(5)} = 7.28$, $p = .0008$, $d = 2.97$) or over the right hemisphere (mean [SD] = –98.2 [33.8] ms, $t_{(5)} = 8.10$, $p = 0.0005$, $d = 3.31$), compared to when TMS was not applied (mean [SD] = –25.8 [19.8] ms).

5.5.3.4 Median cycle velocity

When examining median cycle velocity, as expected, a higher velocity was observed at wrist flexion, when the finger was moving downward (mean [SD] = 40.6 [9.40] cm/s) compared to wrist extension, when the finger was moving upward (mean [SD] = 34.5 [5.81] cm/s, $F_{(1,5)} = 23.73$, $p = .0046$, $\eta_G^2 = 0.14$). The interaction between Tapping and Phase, instead, did not pass the threshold for significance testing ($F_{(1,5)} = 0.20$, $p = .67$, $\eta_G^2 = 0.003$).

5.6 Discussion

In this experiment, TMS was applied over the left and the right cerebellar hemispheres, to examine whether magnetic stimulation could be used to directly interfere with finger-tapping performance. This experiment was inspired by the study of Spencer and colleagues (2003), who reported an increase in tapping variability restricted to the limb ipsilateral to the lesion in unilateral patients with cerebellar ataxia. Given that each cerebellar hemisphere is responsible for the movements of the ipsilateral side of the body, I expected to observe an increase in finger-tapping variability when stimulating the right, but not the left cerebellar hemisphere, compared to when TMS was not delivered. In order to explore the effect of magnetic stimulation at different phases of the movement, TMS was delivered both at wrist extension and at wrist flexion. The effect of cerebellar TMS on different tapping modes was also examined, by asking participants to tap in an intermittent and in a continuous manner in different sessions. Based on Spencer et al., 2003, I expected TMS to affect intermittent tapping to a greater extent than continuous tapping.

I first examined the local effect of TMS on mean ITI and zoomed-in on the ITI around the time of TMS. When TMS was delivered at wrist flexion, with the finger moving downward, the effect of TMS was hemispheric-specific. As shown in **Figure 5.2, panel A**, when TMS was applied over the right CB, only the first ITI following TMS was shorter compared to the no-TMS condition, and tended also to be shorter compared to when TMS was applied over the left CB, this similarly for intermittent and continuous tapping (**Figure 5.2, panels B and C**).

When TMS was delivered at wrist extension, with the finger moving upward and before the pause, the pattern of results differed for continuous and intermittent tapping. While continuous tapping was relatively unaffected by TMS, in intermittent tapping the pace slowed down at the time of TMS, then sped up for the following two intervals. When I compared the pattern of results for intermittent and continuous tapping across TMS condition, with TMS over the left and the right cerebellar hemispheres and without TMS, I noticed that the effect was present only when TMS was applied, but was not hemispheric-specific. In accordance with the clinical study of Spencer et al. (2003) intermittent tapping was more affected by TMS, compared to continuous tapping. However, this effect was not hemispheric-specific, since a similar profile was observed with TMS over the left and the right cerebellar hemispheres (**Figure 5.3**). This result suggested that the local disruption in finger-tapping was unlikely to result from a direct interference of TMS with cerebellar function, but rather could be the effect of other confounding factors, such as nerve and muscle stimulation or a startle effect.

When I looked at tapping variability measured over the whole trial I observed that, when TMS was delivered over the left cerebellar hemisphere, intermittent tapping was more variable than continuous tapping (**Figure 5.4**). Once again, this effect of TMS was not hemispheric-specific, since there was no difference, either for continuous or intermittent tapping between TMS over the right or the left cerebellar hemispheres.

TMS over the left CB was originally designed as a control condition. Any effect observed regardless of the site of stimulation cannot be interpreted as a direct interference of TMS with hemisphere-specific cerebellar function. The effects reported, in fact, could be more easily explained by confounding factors, such as discomfort, a startle effect, or muscle contraction induced by nerves stimulation.

An hemispheric-specific effect, despite directly simulating the cerebellum could be missed if: 1) both the left and the right hemispheres were involved in right-hand finger-tapping to some extent; 2) TMS over the left cerebellum stimulated also the right cerebellum; 3) structures close to the midline are involved; these alternatives cannot be ruled out, given the large size of the double-coil, relative to the distance between the areas stimulated. Notice, however, that while the effect of TMS at flexion tended to be larger for TMS over the left hemisphere, compared to the right, vice versa was true for TMS at extension. Therefore it seemed interesting to examine to what extent this hemispheric lateralization depended on the effector used in finger-tapping.

A second experiment was carried out, to examine any hand-lateralization, comparing the effects of left and right cerebellar TMS over left- and right-hand tapping, when TMS was delivered at wrist extension. The effect of TMS at flexion, despite being the only hemispheric-specific effect observed, could not be examined within the same experiment, due to time limits. I preferred to look at TMS at extension, because the focus of the work was on the dissociation between intermittent and continuous tapping and TMS delivered at extension, but not TMS at flexion, disrupted intermittent tapping more than continuous tapping.

5.7 Methods

5.7.1 Participants

Eight participants were recruited. Two were excluded for unmet inclusion criteria, leaving a sample of 6 (4 female, 6 right-handed, mean ± SD age = 21.8 ± 2.48 years). Two of the participants included participated also in experiment 5.1.

5.7.2 Magnetic stimulation

The mean [SD] head size was 34.6 [0.61] cm from nasion to inion and 36.2 [1.30] cm from left to right pre-auricular points. Stimulation intensity for the experiment had mean [SD] of 62.5 [2.74] % of MSO. Brainstem evoked MEPs, however, were identified in 1/6 participants.

5.7.3 Procedure

The second experiment was similar to the first. Participants took part in two sessions, run on separate days (mean [SD] = 6.8 [8.8] days in between). Half of the participants started with continuous tapping and the other half with intermittent tapping. TMS was always delivered at wrist extension. A mean [SD] of 5.44 [0.49] TMS pulses were delivered on each trial. Within each block, participants tapped with their right hand in half of the trials, and with the left in the remaining half (Hand: right, left).

5.8 Analysis

The analysis is structured as in experiment 5.1. The short-lasting effect of TMS was examined, firstly, by analysing all the data collected in the second experiment and comparing right-hand and left-hand tapping; secondly, using only the data for right-hand tapping, in order to examine whether the effect found in the first experiment replicated. The global effect of TMS on finger-tapping behaviour was also examined, mainly to compare tapping variability across conditions.

5.9 Results

5.9.1 Intermittent and continuous tapping

Classification performance with logistic regression and linear SVM were comparable ($t_{(7)} = 0.33$, $p = .75$, $d = 0.12$). Participant S4 had AUCROC < 0.65 and was excluded from the analysis (AUCROC of 0.567 with logistic regression and 0.576 with SVM). In Participant S5 the expected difference between continuous and intermittent tapping was inverted, therefore he was also excluded from the analysis, despite an above threshold separation between the two classes. This may be due to a misunderstanding in the communication or the reception of task instructions. Importantly, the distinction between intermittent and continuous tapping was examined solely to make sure that participants executed the task correctly, therefore this exclusion did not affect the main hypothesis tests.

On average the pauses up, mean [SD] = 246 [65.0] ms, lasted longer than the pauses down, mean [SD] = 74.9 [61.8] ms (main effect of Pause: $F_{(1,5)} = 20.8$, $p = .006$, $\eta_G^2 = 0.72$). The duration of the pauses up was longer in intermittent tapping (mean [SD] = 292 [35.9] ms) compared to continuous tapping (mean [SD] = 199 [52.8] ms, interaction TappingxPause: $F_{(1,5)} = 19.1$, $p = .007$, $\eta_G^2 = 0.1$, $t_{(5)} = 4.33$, $p = .007$, $d = 1.77$).

5.9.2 Local effect of TMS

In the analysis of the local effect of TMS, 7.04 % pulses were discarded, over the total number of TMS pulses delivered, because they were not followed by at least two taps. A further 3.33 % were discarded because they were not followed within 2/3 of a cycle by a pause.

When the values for mean ITI were entered in a repeated-measured ANOVA with TMS, ITI to TMS, Tapping and Hand as within-participants factors, the interaction between TMS and ITI to TMS passed the threshold for significance testing ($F_{(6,30)} = 3.81$, $p = .006$, $\eta_G^2 = 0.10$): the mean of ITI measured at lag-0 from the TMS pulse was shorter when TMS was applied over the head (right CB: mean [SD] = 703 [33.6] ms, left CB: mean [SD] = 704 [40.6] ms) compared to when TMS was not applied (mean [SD] = 744 [1.1] ms, $t_{(5)} = 2.91$, $p = .033$, $d = 1.19$ and $t_{(5)} = 2.35$, $p = .065$, $d = 0.96$). This effect was not hemisphere-specific, since TMS over the left and the right CB were comparable. ($t_{(5)} = 0.20$, $p = .85$, d

= 0.08). Most notably, this pattern of results did not differ between left-hand and right-hand tapping (TMS, Hand and ITI to TMS: $F_{(6,30)} = 0.18$, $p = .98$, $\eta_G^2 = 0.001$, **Figure 5.5, panel A and B**).

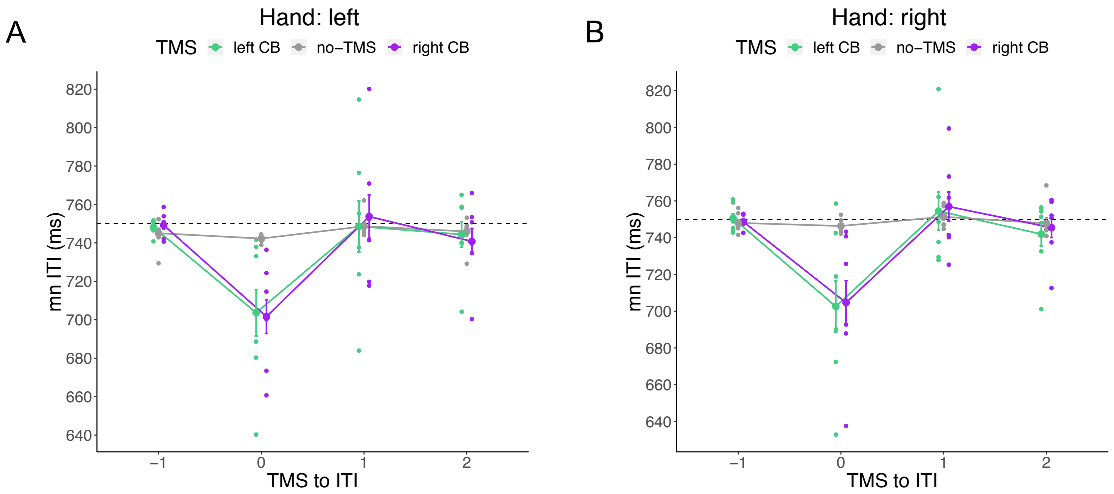


Figure 5.5 *Mean ITI from one inter tap interval (ITI) preceding (–1 on x-axis) up to two ITI following a TMS pulse (0, 1, 2 on x-axis), with TMS delivered at wrist extension with TMS over the left and right cerebellar hemispheres (CB) and when TMS was not delivered (no-TMS): left-hand tapping (A) and right-hand tapping (B). Error bars are 95% between-participants confidence intervals.*

No effect involving Tapping reached significance (all ps > 0.33). The pattern of results for intermittent and continuous tapping, for right-hand tapping only are reported in **Figure 5.6, panels A and B**, to facilitate the comparison with experiment 5.1, **Figure 5.2, panels B and C**.

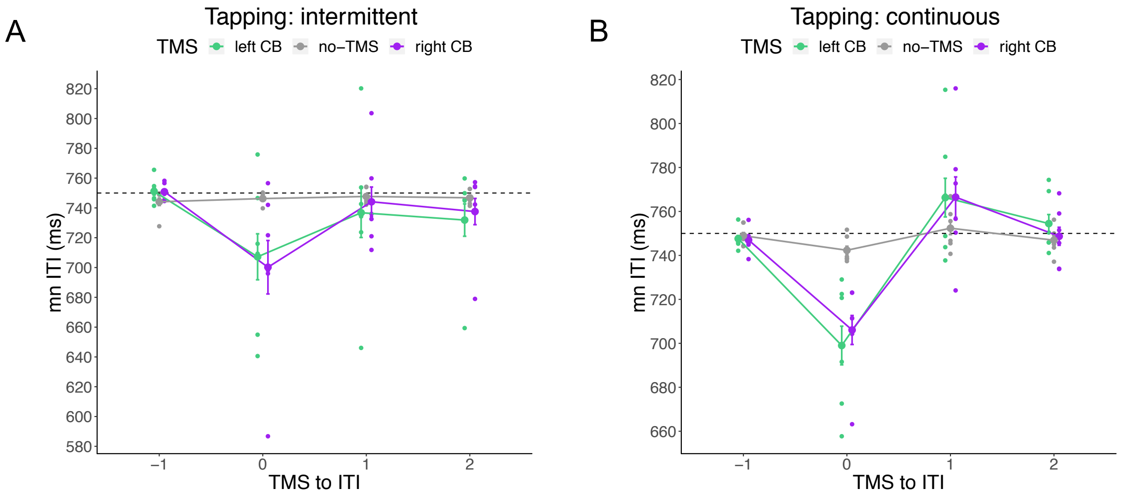


Figure 5.6 *Mean ITI from one inter tap interval (ITI) preceding (–1 on x-axis) up to two ITI following a TMS pulse (0, 1, 2 on x-axis), with TMS delivered at wrist extension for intermittent tapping (A) and continuous tapping (B) compared across TMS conditions. Error bars are 95% between-participants confidence intervals.*

5.9.3 Global effect of TMS

5.9.3.1 Mean and coefficient of variation of ITI

TMS did not significantly affect mean ITI, or the coefficient of variation of ITI measured over the whole trial (all ps > .09). The only effect that passed the threshold for significance testing was the main effect of Hand for the coefficient of variation of ITI ($F_{(1,5)} = 7.96$, $p = .037$, $\eta_G^2 = 0.04$), indicating that tapping variability was higher for left-hand tapping (mean [SD] = 8.10 [2.51] %), compared to the right-hand tapping (mean [SD] = 6.97 [2.00] %). The interaction between TMS, Tapping and Hand for the coefficient of variation of ITI ($F_{(2,10)} = 1.64$, $p = .24$, $\eta_G^2 = 0.01$) is reported in **Figure 5.7**, to facilitate the comparison with experiment 5.1.

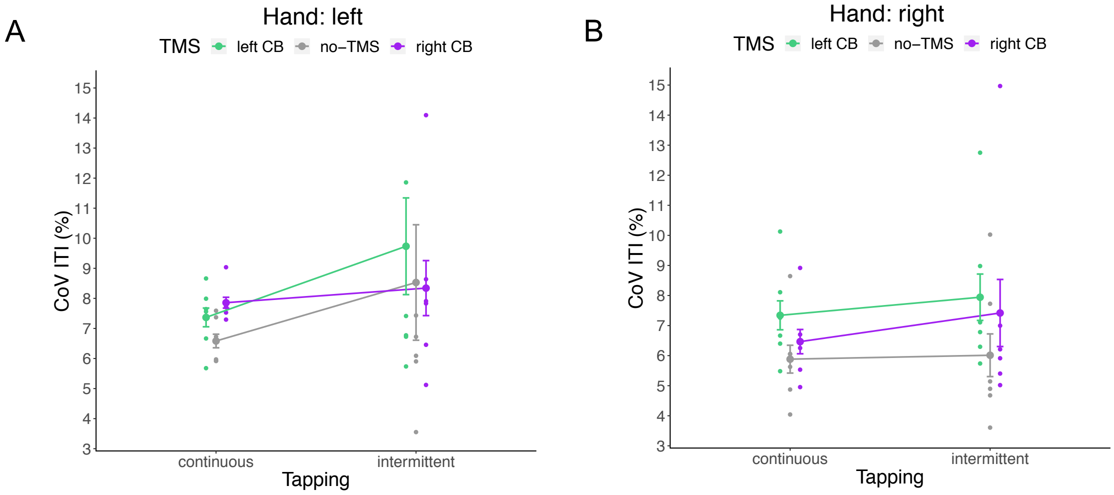


Figure 5.7 *Coefficient of variation of ITI (%) when TMS was applied over the right CB (in purple) and the left CB (in green) and when TMS was not delivered (in grey) for intermittent and continuous tapping for left-hand tapping (A) and right-hand tapping (B). Error bars are 95% between confidence intervals.*

5.9.3.2 Median cycle velocity

When examining median wrist velocity, as expected, a higher velocity was observed at wrist flexion (mean [SD] = 47.6 [11.6] cm/s) compared to wrist extension (mean [SD] = 35.9 [7.41] cm/s, $F_{(1,5)} = 34.77$, p = .002, $\eta_G^2 = 0.3$). Critical to the study, median velocity for the upward and downward phases were comparable between continuous and intermittent tapping (Tapping X Phase: $F_{(1,5)} = 3.44$, p = .123, $\eta_G^2 = 0.01$). Median velocity, however, was affected by TMS ($F_{(2,10)} = 14.6$, p=.0011, η_G^2=0.01): the downward movement was faster when TMS was applied over the left (Mean [SD] = 49.4 [9.05] cm/s) than the right cerebellar hemisphere (Mean [SD] = 48.9 [9.03] cm/s, $t_{(5)} = 2.98$, p = .03, d = 1.22); and in the TMS compared to the no-TMS condition (Mean [SD] = 44.5 [9.98] cm/s, left: $t_{(5)} = 5.66$, p = .0024, d = 2.31 and right: $t_{(5)} = 4.49$, p = .0065, d = 1.83).

5.10 Discussion

The purpose of this second experiment was to examine any hand-lateralization in finger-tapping performance. In experiment 5.2, TMS produced a measurable local effect on the taps around the time of stimulation. This effect was comparable between right-hand and left-hand tapping. Once again this effect was not hemispheric-specific. Besides, the pattern of results for this effect was qualitatively different from the pattern observed in experiment 1. The difference can be appreciated by comparing **Figure 5.2** (**panels B and C**) and **Figure 5.6**. A global effect of TMS was not observed in experiment 5.2.

5.11 Conclusions

Cerebellar TMS was expected to produce a global increase in tapping variability when stimulating the right, compared to the left cerebellar hemisphere. Based on the results from the clinical study of Spencer and colleagues (2003), a larger increase in tapping variability was also expected for intermittent tapping, compared to continuous tapping. According to these predictions, in experiment 5.1 a global effect was observed in intermittent tapping, compared to continuous tapping. However, the increase in tapping variability was comparable between TMS over the left and the right cerebellar hemispheres, despite the fact that the perturbation was TMS-specific. Notice also that in experiment 5.2 a similar global effect was not observed. As previously explained, TMS over the left cerebellum was chosen as a control condition, therefore any effect observed regardless of the site of stimulation can be explained by confounding factors, rather than by a direct interference of TMS with hemisphere-specific cerebellar functions. From this consideration, the local effects observed in experiment 5.1 and 5.2 were likely to be the result of a startle effect induced by noise and abrupt discomfort, and by the stimulation of peripheral muscles. While running the experiments, an attempt was made to limit peripheral stimulation, by visually monitoring the EMG signal recorded from right arm muscles. However, depending on the particular fit between the large double-cone coil and the head of the participant, it has not always been possible to avoid for the coil being in contact with the back of the neck. Therefore it cannot be excluded that TMS targeted at the lateral cerebellum stimulated also neck nerves and neck and shoulder muscle, thus directly affecting movement kinematics. Most importantly, during the experiment it has not been possible to control for the level of discomfort or for the non-habituating TMS-induced startle-like reflex, which alone has been shown to affect movement kinematics (Xu-Wilson et al., 2011). For all these reasons, most likely it was a direct effect from TMS on the kinematics that led to the observed changes in mean ITI. Notice also that TMS pulses were delivered at a random delay (this both for TMS at flexion and at extension), which implies that the movement trajectory with each TMS pulse was perturbed at a different point in time, thus adding variability to the effect of TMS on the movement kinematics. Increased variability in the observed values of mean ITI (especially at lag 0 and 1) introduced by delivering TMS pulses at random intervals, may have made it more difficult to characterise any effect of TMS. This in part may explain why the results from experiment 5.1 did not replicate in experiment 5.2.

To conclude, in the work reported in this chapter, single pulse TMS was used in an attempt to interfere with finger-tapping performance, by stimulating the cerebellar hemisphere ipsilateral to the moving hand. The two experiments reported were carried out to examine whether the cerebellum plays a critical role in auditory-motor synchronisation. At the time of writing and to the best of my knowledge, only one published study reported a successful attempt to interfere with finger-tapping synchronisation, using cerebellar (repetitive) TMS (del Olmo et al., 2007). In the present work, TMS had an effect on finger-tapping performance, but the effect was short-lasting and non-hemispheric specific, therefore it was unlikely to have resulted from a direct effect of the stimulation with cerebellar function. For this reason, the work reported in this chapter did not provide an answer to the research question addressed.

Chapter 6. Function of the cerebellum in intermittent and continuous auditory-motor synchronisation: an fMRI study.

6.1 Abstract

The cerebellum is thought to play a critical role in timing and rhythmic auditory-motor synchronisation, abilities considered at the basis of complex behaviours like dance, music and speech perception and production. In the context of auditory-motor synchronisation, a dissociation has been proposed between intermittent movements, interrupted by pauses at each cycle, and continuous movements. The leading hipothesis is that the brain relies on the cerebellum for the execution of temporally contrained intermittent movements, while rhythmic continuous movements do not require temporal processing for correct execution. A previous functional MRI study reported increased functional activation in response to intermittent, comapared to continuous movements, but the result is confounded by differences in the motor component of the task, which is known to correlate with functional activation in motor regions. A simultaneous EMG-fMRI experiment targeting the cerebellum was carried out to examine further the proposed dissociation between intermittent and continuous rhythmic movements. The ability for auditory-motor synchronisation was studied at difference task requirements, where the movements could be either paced by an external auditory metronome or unpaced. Representational similarity analysis (RSA) was used to test whether functional activation in the cerebellum was more likely to reflect the achievement of the synchronisation goal, rather than the motor demands of the task. Continuous movements activated cerebellar lobules VI and VIIIb more than intermittent movements and functional activation was more likely to reflect the motor demands of the task, rather than processing specific to the achievement of the sychronisation goal.

6.2 Introduction

In motor-control research, complex behaviours like music production and dance are thought to rely on the auditory-motor synchronisation ability. Auditory-motor synchronisation requires moving a limb, bringing it periodically to a given spatial location, in some temporal relation with an external auditory stimulus. This is typically studied with the finger-tapping task (see Repp, 2005a; 2013 for a review).

This chapter addresses the debate in motor control research, about the distinction between intermittent (often referred to as “discrete”) and continuous rhythmic movements in auditory-motor synchronisation. The matter of this debate is whether intermittent and continuous rhythmic movements require distinct motor-control mechanisms and whether these mechanisms are implemented by distinct neural structures in the brain.

A dissociation between intermittent and continuous rhythmic movements was proposed by Zelaznik and colleagues, who observed that the variability of the intervals between consecutive taps measured for intermittent movements did not correlate with the inter-tap-interval for continuous movements (Zelaznik, Spencer & Doffin, 2000; Zelaznik, Spencer & Ivry, 2002). A similar result was found with variations of the task used for intermittent movements (i.e., finger-tapping against a surface, intermittent finger-tapping, or cycle-drawing in the air) and continuous movements (i.e., continuous finger-tapping or circle-drawing in the air).

The dissociation between intermittent and continuous rhythmic movements is supported also by clinical study on sensorimotor synchronization in cerebellar ataxia (Ivry, Spencer, Zelaznik & Diedrichsen, 2002; Spencer, Zelaznik, Diedrichsen, & Ivry, 2003). In these studies, patients with cerebellar ataxia performed worse than healthy controls when executing intermittent movements, but were spared in continuous movements, as measured with a synchronisation-continuation task. These studies provided some evidence for a role of the cerebellum in this dissociation.

For a long time, intermittent and continuous rhythmic movements have been studied by research communities with a different theoretical approach and a preferential type of analysis. Intermittent movements have been the focus of researchers with an information-processing, and have been described in terms of timing processes (e.g., Vorberg and Wing, 1996). These studies focused on how the timing goal was achieved, looking at the time intervals between cycles and at timing errors. Continuous movements, instead, were primarily studied in terms of within-cycle dynamics in movement trajectories, from a dynamical-system approach. Researchers belonging to this second class were interested in how coordination is achieved. They treated timing as an emergent property of the motor system (e.g., Schöner and Kelso, 1988). In the end, the two lines of studies converged (Balasubramaniam et al., 2004; Balasubramaniam, 2006; Torre and Blasubramaniam, 2009). Movement trajectories in intermittent and continuous rhythmic synchronization were shown to be linked to the achievement of a timing goal. Nevertheless, some have argued in favour of a dissociation between intermittent and continuous rhythmic movements, and for them requiring distinct mechanisms (Torre and Blasubramaniam, 2009; Howard, Ingram & Wolpert, 2011).

In an attempt to localize in the brain the cognitive processes involved in intermittent and continuous movements, neuroimaging techniques have been used. Schaal, Sternard, Osu, and Kawato (2004) compared blood-oxygen-level-dependent (BOLD) activation in response to intermittent (called discrete) and continuous flexion-extension wrist movements. Continuous movements were rhythmic, and the frequency was imposed by an external auditory cue, while intermittent movements were non-rhythmic and free from temporal constraints. Further, continuous movements were initiated once per trial by an external auditory cue, while intermittent movements involved multiple movement onsets, either self-chosen at random times (Schaal et al.'s Experiment 1 and 2) or imposed by an external cue (their Experiment 3). Functional activation unique to intermittent movements was found in premotor dorsal (PMd) and in Brodmann Areas (BA) 7 and 47. The activation unique to intermittent movements, however, was suggested to reflect a higher demand placed on cognitive processing by this task, as compared to the continuous task.

In a similar attempt, Spencer, Verstynen, Brett and Ivry (2007) examined intermittent and continuous movements with a continuation task, where the movements were unpaced and the rhythm had to be internally generated. In this study participants tapped their finger in an intermittent manner, inserting a pause between finger extension and finger flexion, or in a continuous, smooth manner. The authors observed that the cerebellar lobules V/VI of the superior vermis were more active in intermittent compared to continuous tapping. However, as the authors pointed out, BOLD activation is known to increase with movement frequency, therefore the differences in the functional activation may simply be attributed to differences in movement kinematics.

With the neuroimaging work presented in this chapter I aimed at examining further the dissociation between intermittent and continuous rhythmic movements, with a focus on the cerebellum. This aim is challenging, because intermittent and continuous movements, by definition, are expected to differ in terms of movement kinematics. While intermittent movements are characterized by larger peaks in velocity, compared to continuous movements of the same overall frequency, the mean movement velocity for a given movement rate is expected to be higher in continuous, compared to intermittent movements. This difference alone will likely be reflected in the functional activation of motor regions in the brain, both in the neocortex and the cerebellum (see Deiber et al., 1999, Jäncke et al., 1999, Sadato et al., 1997).

In order to dissociate the neural correlates specific to sensorimotor synchronisation, from the correlates of motor execution, intermittent and continuous rhythmic movements were examined under different task requirements, by using the synchronise and continue versions of the finger-tapping task (Spencer et al., 2003). In the synchronise task, movements were paced by a metronome - a sequence of regularly spaced sounds; in the continue task, movements were unpaced, and the rhythm had to be internally generated, at the same pace as a previously cued rhythm.

In the experiment presented here, unlike in Schaal et al. (2004), intermittent and continuous movements were both rhythmic; these were examined under different task requirements, rather than at different movement rates like in Spencer et al. (2007). The continuous movements were changed with respect to those used in **Chapter 5**, from vertical linear movements to circular movements. This new version of the task was easier to explain, and for the participants to understand and perform correctly, and resulted in distinct cycle profiles (see **Section 6.5.1**). This choice was inspired by the work of Torre and Balasubramaniam (2009). Inside the scanner all, movements were monitored by recording the electromyography (EMG) signal acquired from the First Dorsal Interosseous (FDI) muscle, simultaneously with fMRI acquisition. This signal allowed comparison between motor output and brain activity in task-related motor regions (van Rootselaar et al., 2007). As a further development from the previous studies, functional image acquisition targeted the cerebellum, which is suggested to be involved in the intermittent–continuous dissociation, but that is often neglected in functional MRI studies. Despite all these changes, it was still not possible to completely avoid differences in the purely motor component of the task across conditions. Notice that even the paced and unpaced tasks were likely to differ in terms of movement kinematics, to some extent. In fact, in the unpaced task, in the absence of a pacing stimulus, one may expect to observe a more variable inter-tap-interval.

Representational similarity analysis (RSA) was used in an attempt to overcome this limitation. First, RSA was used to examine whether intermittent and continuous rhythmic movements, both paced by a rhythmic auditory stimulus and unpaced, could be resolved into distinct patterns of blood-oxygen-level-dependent (BOLD) response, within the cerebellar lobules of interest. Second, competing theoretical and behavioural models were tested on the functional data and compared with each other. More specifically, RSA was used to test whether the distinction between movement types and the paced and unpaced tasks was encoded in the functional activity of the cerebellum. Moreover, alternative behavioural models were tested to decide whether the cerebellum was more likely to encode aspects specific to the achievement of the timing goal, rather than motor execution per se.

6.3 Methods

6.3.1 Participants

Twenty-nine participants were recruited for the behavioural session. Two of them were excluded, one because they became impatient and could not tolerate the task, another because of poor performance, leaving a sample of 27 participants (16 females, 3 left-handed, M ± SD age = 24.1 ± 4.42 years). Thirteen participants took part in a subsequent fMRI session. Twelve of them were selected among the participants from the behavioural session, based on their task performance (see below) and one was the author. One participant was excluded, due to magnetic susceptibility artefacts in the functional scans, leaving a sample of 12 (6 females, all right-handed, M ± SD age = 23.9 ± 2.69 years). All participants provided written informed consent and took part in the experiment in return for payment (£17). Among the participants who took part in the functional MRI session, 10 played a musical instrument; the mean ± SD age of start was 9.55 ± 4.16 years. Six of them reported to have taken music lessons, studying a musical instrument for a mean ± SD of 6.71 ± 3.77 years, and music theory for a mean ± SD of 3.83 ± 1.83 years. Nine participants reported to like dancing. All participants were healthy adults with had normal hearing and no history of audiological or neurological disorder and no current use of any psychoactive medications. The study was approved by the research ethics committee (SoPEC 1080) of the University of Nottingham and was conducted in accordance with the Declaration of Helsinki (as of 2008).

6.3.2 Auditory stimuli

Auditory stimuli were a series of sounds of 50 ms duration (gated on and off with a 10 ms linear ramp), interspersed with blank intervals of 700 ms. The high-pitched sounds had frequency of 330 Hz; the low-pitched sounds of 220 Hz and were sampled at 44.1 kHz. In the behavioural sessions the series of sounds were digitally created with LabView and presented using the built-in audio device and a loudspeaker; in the functional MRI session they were digitally created with Matlab (Mathworks. Natick. USA) and presented binaurally with PsychPortAudio (Psychotoolbox v. 3. Brainard, 1997; Pelli, 1997) using the built-in audio device through MR-compatible headphones. Auditory stimuli were presented inside the scanner through MRI-compatible headphones, at an intensity that was audible to the participant, and above the background scanner noise (~100 dB sound pressure level [SPL]).

6.3.3 Procedure

6.3.3.1 Behavioural session

Participants were instructed on the task, gave their written consent and filled in a questionnaire on musicality (Appendix). They were seated on a swivel chair and had their right arm resting over a foam pillow, with the hand extending beyond it. Four electrodes were placed in pairs on the right FDI and on the right EDC muscles. The electrodes were positioned over the muscle's belly at 2 cm distance from each other. A Velcro strap ground electrode attached to the wrist was used as a reference. One motion tracker was attached to the right index finger (see **Chapter 3**, **Section 3.3.2**). At the start of each trial, a vocal instruction (i.e., "continuous" or "intermittent") was presented, to inform participants on the movement type for the following trial. Participants were required to move their finger in a continuous or in an intermittent manner, executing oscillatory movements in the air. In intermittent movements participants were asked to move their finger up and down, inserting a pause at full finger extension of each movement cycle (i.e., intermittent finger-tapping). In continuous movements, they were asked to draw smooth circles in the air and moved their finger in a circle, keeping the movements uninterrupted (see **Figure 6.1**).

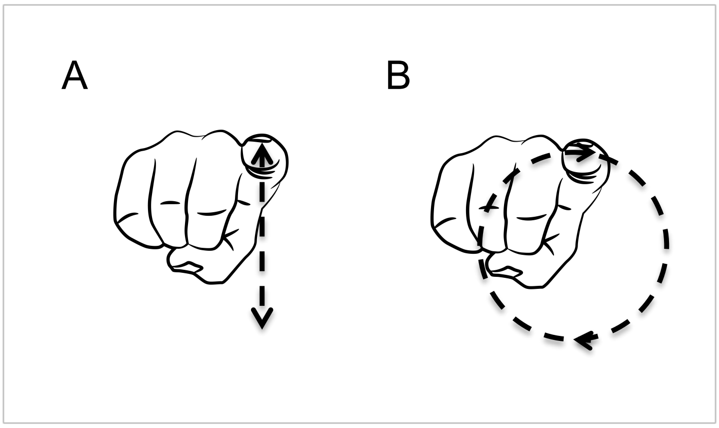


***Figure 6.**1 Schematic representation for movement type: A) intermittent movements (i.e., finger-tapping, interrupted at each semi-cycle); B) continuous movements (i.e., smooth circle-drawing).*

After the task instruction, participants listened to an isochronous sequence of 5 low-pitched sounds. In half of the trials, 30 additional similarly-spaced high-pitched sounds were presented and participants were required to tap in synchrony with the beat, reaching full finger flexion on the beat and full finger extension on the offbeat (paced task). In the other half of the trials, only one pair of high-pitched sounds was presented, to mark the start and the end of the moving phase. Participants were required to execute periodic movements at the same tempo as the sounds played during the listening phase, without the support of an external metronome (unpaced task, see **Figure 6.2**). Participants completed 5 blocks of 12 trials. All conditions were presented in pseudo-random order within each block of trials.

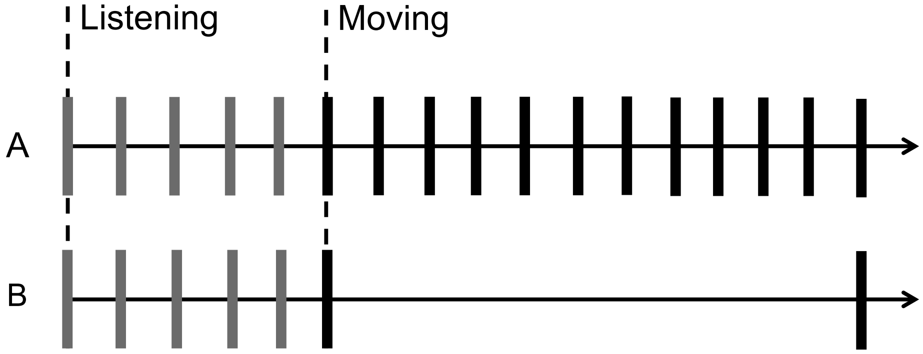


Figure 6.2 *Schematic representation of auditory stimuli for Task: A) in the synchronise task finger movements were paced by the metronome; B) in the continue task where finger movements were unpaced and the rhythm had to be internally generated. During the moving phase, participants executed 30 movement cycles in the behavioural session and 12 in the fMRI session.*

6.3.3.2 Functional MRI session

Participants filled in the MRI safety questionnaire and changed into scrubs. One pair of bipolar MRI-compatible electrodes was placed over the right FDI. A reference electrode was positioned over the right wrist and a ground electrode was placed over the right elbow joint (see **Chapter 3**, **Section 3.3.1**). Inside the scanner, a pillow was placed under the participant's right arm, so that the hand was lifted-up from the chest, to facilitate movements of the finger. At the start of a trial, a written instruction (i.e., "continuous", coloured in emerald or “intermittent”, in orange) was presented centrally on a back-projection screen, which was seen through a mirror. The instruction was presented for 1500 ms and informed participants on the task for the upcoming trial. After 500 ms the low-frequency sounds were played, similarly as in the behavioural session; the moving phase followed at 3700 ms and participants executed 12 movement cycles. A filled circle, colour-coded as the instruction, was presented centrally for 8000 ms, to remind participants they were in an intermittent or in a continuous trial. Consecutive tapping phases were separated by 20 seconds. Each session comprises 8 runs of 12 trials. The 4 conditions were presented in pseudo-randomized order for 3 times within each run, consistently with an event-related design.

6.3.4 MRI image acquisition

MRI was performed on a Philips 3 T Achieva scanner (Philips, Best, Netherlands) with a 32-channel head coil. An average of 6 (range 4–8) partial-brain functional scans were acquired with a 2D echo planar imaging (EPI) sequence (2.664 s repetition time [TR], 35 ms echo time [TE], 2.5 mm isotropic resolution, 80° flip angle, 96x96 matrix, 43 slices acquired in interleaved order). The functional scans for the first two participants were acquired at different sequence parameters (2.881 s TR, 40 ms TE).

Repetition time and TE were changed at the third acquisition, in an attempt to improve temporal resolution and signal-to-noise ratio. Near-coronal slices were used so that the region of acquisition included cerebellum, basal ganglia and primary sensorimotor cortex in full, and maximized coverage of supplementary motor area (SMA) and premotor cortex (see **Figure 6.3** for an example).

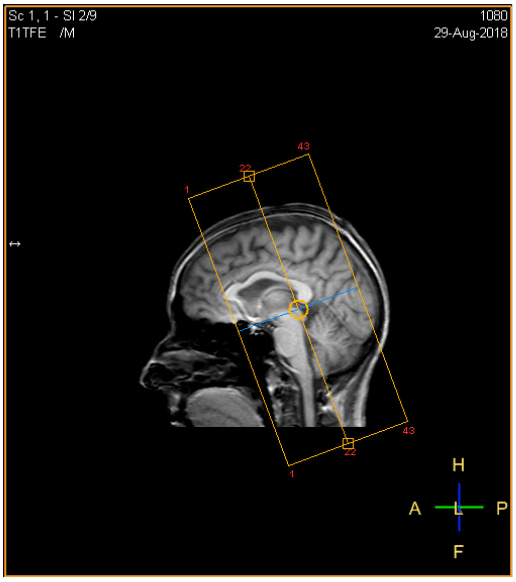


Figure 6.3 *Example for planning of partial-brain functional EPI that shows the region of acquisition included in the near-coronal slices (i.e., area inside the rectangular box).*

A whole-brain structural scan (6.8 ms TR, 3.1 ms TE, 1 mm isotropic resolution, 256x256 matrix, 180 slices) was acquired using a magnetization-prepared rapid gradient echo (MPRAGE) sequence. A whole-brain functional scan at rest, with the same parameters as the partial brain scan, was acquired to improve the registration between partial-brain and structural scans. The full MR scanning protocol lasted 60 mins.

6.4 Analysis

The analysis section is structured into 5 main sub-sections. The first sub-section (**6.4.1**) includes a description of the tests run to check: 1) whether participants executed intermittent and continuous movements correctly, with longer pauses for intermittent, compared to continuous movements; 2) whether the two movement types were similar to the movements studied by Torre and Balasubramaniam (2009). Based on their study, I expected to observe a more asymmetrical position-velocity profile and larger negative values for lag-1 autocorrelation function (ACF), for intermittent as compared to continuous movements.

Section 6.4.2 includes a description of how differences in auditory-motor synchronisation performance across tasks were assessed; **Section 6.4.3** describes a similar test run to compare peak and mean cycle velocities across tasks.

The fourth sub-section (**6.4.4**) includes a description of how the EMG signal was used in the behavioural and the functional MRI analyses. This part starts with common pre-processing steps and is followed by analysis steps specific to the behavioural and the fMRI sessions. In the behavioural session, the EMG signal was used to calculate an estimate of movement rate and to test the agreement between this measure and an analogous measure, derived from the position of the index finger recorded with motion-tracking. This analysis was run in preparation for the fMRI session, where only the EMG signal was available. In the fMRI session, the EMG signal was used as a nuisance regressor in univariate analysis, as well as to build two behavioural models that were used as predictors in representational similarity analysis (RSA).

The last sub-section (**6.4.5**) was dedicated to neuroimaging analysis and includes a description of univariate analysis and RSA. Univariate analysis was run to examine which cerebellar lobules were activated by the tasks, as well as any differences in the distribution of activation between movement types (intermittent; continuous) and tasks (paced; unpaced). RSA was used to examine whether the differences between tasks were represented in the activity patterns for the cerebellar lobules of interest (lobules V, VI and VIII, ipsilateral to the moving hand) and to test whether these patterns were more likely to represent the achievement of a timing goal, rather than the motor demands of the task.

6.4.1 Intermittent and continuous rhythmic movements

Pause duration. The difference between intermittent and continuous movements was first examined by looking at the duration of the pauses at full finger extension (finger up) and at full finger flexion (finger down). In the intermittent task, participants were instructed to execute discontinuous movements; therefore the duration of the two pauses (up and down) should be longer, compared to the continuous task. The pauses were defined as the longest continuous intervals with movement velocity < 3.5 cm/s. The duration of the longest pauses up and down were calculated for each tapping cycle, averaged within trials and compared across movement types.

P*osition-velocity profiles.* To further examine the distinction between intermittent and continuous movements I looked at the position-velocity profiles, as done by Torre and

Balasubramaniam (2009), looking for asymmetries in the profile of intermittent tapping and for a more symmetrical profile for continuous tapping. The difference in these profiles was quantified here with the (a)symmetry in the peak velocity for the upward and the downward phases of a finger-tapping cycle. Peak velocity asymmetry was calculated cycle-by-cycle, as the difference between peak velocity for the downward and the upward phases, divided by the sum of the two peak velocities. The values for pause duration and peak velocity asymmetry were averaged across trials compared across the movement types.

Lag-1 autocorrelation function (ACF). A third hallmark of intermittent and continuous rhythmic movements is provided by the lag-1 autocorrelation function (ACF) of the times between consecutive taps (or ITIs). Similarly, intermittent and continuous rhythmic movements paced by an auditory stimulus were shown to be associated with a negative and a non-negative lag-1 autocorrelation respectively (Torre & Balasubramaniam, 2009; but see also Delignières et al. 2008; Lemoine and Delignières 2009; Torre and Delignières 2008). A negative autocorrelation of the inter-tap-interval shows that each finger tap is affected by the previous tap and therefore is an index of tap-to-tap error correction. Based on these previous studies, I expected to observe a more negative ACF for intermittent, compared to continuous paced movements. Moreover, I expected to find a larger difference between movement types when the movements were paced by an external metronome, compared to when they were unpaced. The values for lag-1 ACF were averaged across trials and entered in a repeated-measures ANOVA with Task (paced, unpaced) and Movement Type (intermittent, continuous) as within-participants factors.

6.4.2 Auditory-motor synchronisation

Performance in the tasks was examined by measuring the inter tap interval (ITI) and the coefficient of variation of ITI (CoV ITI) for all 4 conditions, and the negative asynchronies (NA) for paced movements only (see **Chapter 3**, **Section 3.4**). Mean ITI and CoV ITI were entered separately in a repeated-measures ANOVA with Movement Type and Task as within-participant factors; NAs were entered in a t-test and compared across Tapping. Mean ITI and NA were also used to set the inclusion criteria for the functional MRI session: only participants with mean ITI in the range [700, 800] ms (the target ITI was 750 ms) and NA ≤ 50 ms were considered eligible.

6.4.3 Movements kinematics

Mean velocity and peak velocity for finger-tapping movements were calculated, in order to characterise the 4 conditions in terms of movement kinematics (see **Chapter 3, Section 3.4.4**). The values were entered separately in a repeated-measures ANOVA with Movement Type and Task as within-participant factors. This analysis was run to inform the interpretation of the functional MRI data, and was motivated by the fact that faster movements are associated with a larger functional activation in several motor regions, including the cerebellum (Deiber et al., 1999; Jancke et al., 1999; Sadato et al., 1997; Spencer et al., 2007). Therefore, in order to make inferences on the functional activation in response to different task requirements (i.e., synchronise and continue tasks), it is necessary to account for the functional activation in response to different movements kinematics.

6.4.4 Electromyography (EMG)

Pre-processing. The EMG signal recorded in the behavioural and the fMRI sessions was high-pass filtered with 10 Hz cutoff-frequency to reduce movement-related artefacts, and full-wave rectified, to recover the low frequency content (see van Rootselaar et al., 2007). The EMG signal recorded during the MRI session was first gradient-artefact corrected with BrainVision Analyzer, to remove imaging artefacts, then exported for further processing with a custom Python script using the MNE module (0.17.0 version). Recording the EMG signal inside an MRI scanner can be challenging, because the signal is corrupted by the scanner's magnetic field and radiofrequency pulses, therefore artefact correction is mandatory.

Behavioural session. The EMG signal recorded during the behavioural session was used to estimate the inter-tap-interval (ITI), as an alternative measure of mean ITI based on the finger's position. This estimate was obtained by calculating the power spectrum with the Discrete Fourier Transform (DFT) of the EMG signal recorded during task execution, sampled over a period of 20 seconds (temporal resolution of 50 ms). The frequency at maximum power within the range 0-2.5 Hz was then extracted (the expected tapping frequency was 1.3 Hz).

The agreement between mean ITI based on the EMG signal and mean ITI based on position was calculated, to examine whether the former measure could be used as a surrogate of the latter. This was done in preparation for the fMRI session, where only the EMG signal was available. A measure of the agreement between EMG-based and position-based mean ITI was calculated, separately for the FDI and the EDC muscles, by subtracting position-based mean ITI from EMG-based mean ITI. The agreement was calculated to estimate the degree to which the EMG-based mean ITI was likely to differ from the position-based mean ITI. In order to decide whether there was a good agreement between the two measures, the signed and the absolute distances, which are a measure of bias and error respectively, were entered in a repeated-measure ANOVA with Task, Movement Type and Muscle (FDI, EDC) as within-participants factors. The signed distance values for FDI and EDC were also compared against zero. The absolute distance between the two measures, as an index of error, was used to decide which muscle to monitor in the fMRI session.

Functional MRI Session. The EMG signal recorded during the fMRI session was used in the first-level analysis of the functional MRI data, to identify brain activation related to the motor component of the tasks, and to regress out the activation due to undesired movements in the task's off period (see **Section 6.4.5.1**). The EMG regressors were obtained by pre-processing, mean-normalising and downsampling the EMG signal, to match the TR used for fMRI acquisition (see **Figure 6.4** for an example).

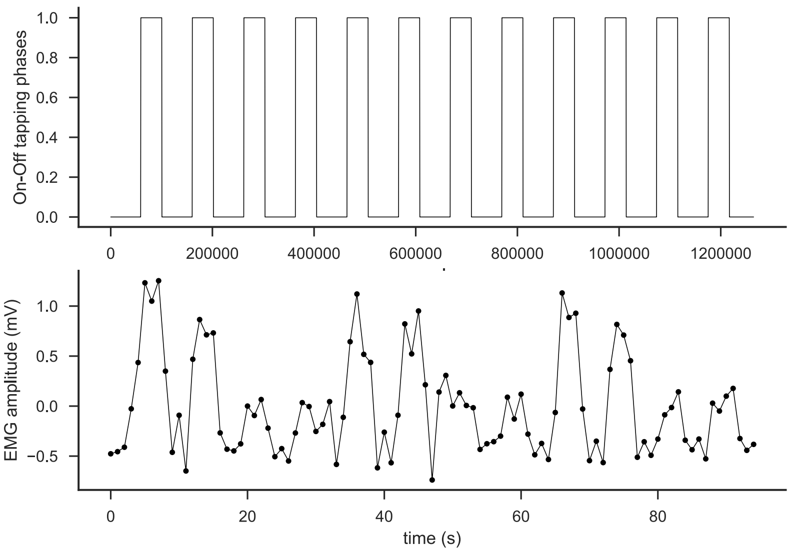


Figure 6.4
Example for EMG regressor: the 12 on-off tapping phases of a run (top); processed down-sampled EMG signal (bottom) used in the GLM analysis.

The EMG signal was also used to construct model representational dissimilarity matrices (RDMs) to be used for representational similarity analysis (RSA) analysis (**Section 6.4.5.2**). A first model was constructed from the EMG-based mean ITI; a second, from the median amplitude of the EMG signal recorded during fMRI acquisition. Mean ITI was computed, similarly as in the behavioural session, from the EMG sampled over an entire epoch, lasting 20 seconds (temporal resolution of 50 ms); median EMG amplitude was calculated by taking the median of the EMG signal recorded during each tapping phase of each trial within a functional MRI run.

6.4.5 Imaging data analysis

The functional data was analysed using SPM12 (https://www.fil.ion.ucl.ac.uk/spm/). The partial-brain functional data was spatially realigned for motion across runs, to the first image of the session, using a six-parameter rigid-body transformation. No slice time correction was applied. The functional data was co-registered to a whole-brain functional, then to a structural scan, and analysed with a generalized linear model (GLM). A high-pass filter was applied with cutoff of 280 seconds (maximum length of time between pairs of epochs of the same condition = 140 s). The four task conditions, the listening phase, and the presentation of the visual task-cue were modelled as on-off boxcar functions, convolved with a canonical dual-gamma hemodynamic response function (HRF). The temporal derivatives for all regressors were included as covariates, to account for any potential lags in the onset of the HRF. The EMG signal recorded during each run simultaneously with fMRI acquisition was entered in the model as a further covariate of no interest, orthogonalised via Gram-Smidth serial orthogonalisation to all other conditions. The SUIT toolbox (Diedrichsen 2006) was used in the analysis of the cerebellum. First, the cerebellum and brainstem in the anatomical scan were isolated from the rest of the brain. Secondly, the isolation map was checked using the FSL image viewer FSLeyes. Thirdly, the cerebellum was aligned to the SUIT template, using the Dartel normalisation method.

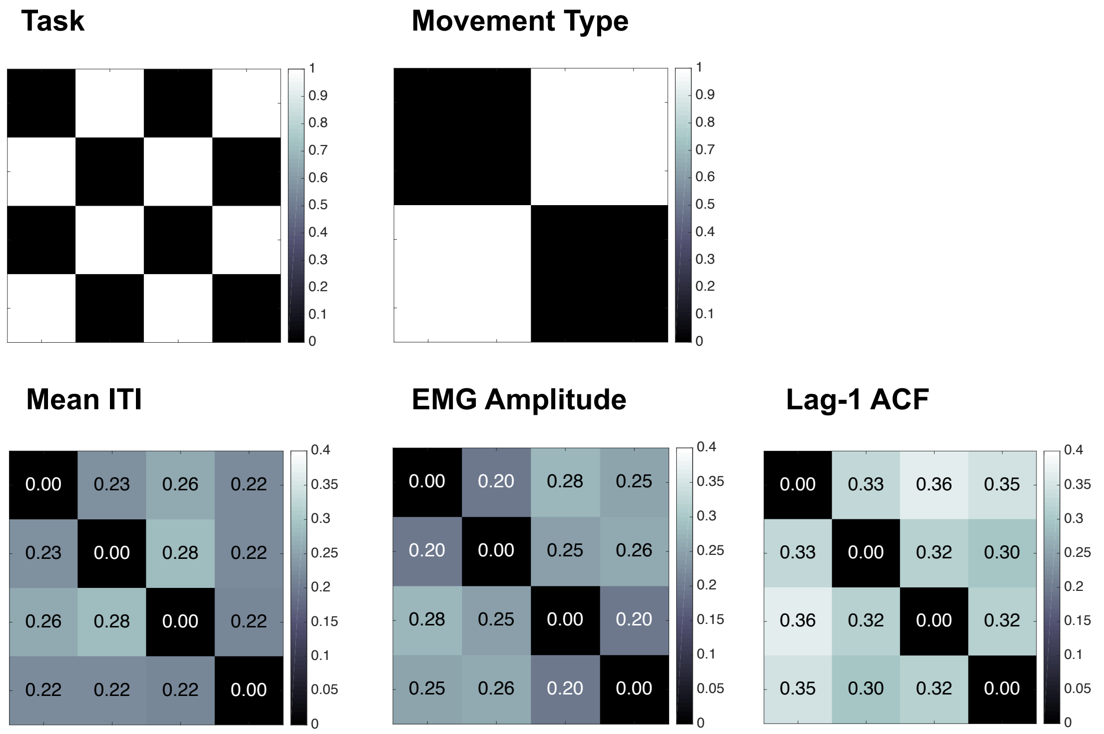
6.4.5.1 Univariate analysis

All 4 conditions were compared against rest, to examine regions of activation common to all conditions. The other pairwise subtraction contrasts considered were, *paced* > *unpaced* and *unpaced* > *paced, intermittent* > *continuous* and *continuous* > *intermittent*. All contrast images, the weighted sums of single beta images, were smoothed with a 5 mm full width half max (FWHM) Gaussian filter, and resliced into the SUIT atlas (1x1x1 mm voxel size) and the MNI atlas (4th degree B-spline interpolation; 2x2x2 mm voxel size), using the output from the normalisation. A random-effect analysis was performed on these resulting images for statistical evaluation. Cluster-wise correction was used to correct for multiple comparisons (Worsley et al., 1996). All clusters were identified at an uncorrected voxelwise threshold of $p < 0.001$, and corrected for multiple comparisons over the volume of the cerebellum with family-wise error (FWE) found by random field theory with SPM ($p < 0.05$). The statistical images resulting from direct subtraction contrasts (e.g., *continuous* > *intermittent*) were masked to avoid significant differences in activation due to negative activity in the control condition. This was accomplished by masking the activity with binarized maps for the significant activity resulting from contrast of the appropriate test versus rest baseline condition (e.g., *continuous_paced* > *rest* V *continuous_unpaced* > *rest*, at voxelwise $p < 0.001$, uncorrected). Cluster maxima were identified using an appropriate atlas; both the anatomical labels and the likelihood for the activation to be in a certain region were reported.

6.4.5.2 Representational similarity analysis (RSA)

RSA analysis was performed in native functional space, using the RSA Matlab toolbox (Nili et al., 2014, http://www.mrc-cbu.cam.ac.uk/methods-and-resources/toolboxes/). In RSA, each experimental condition is associated with an activity pattern, a vector of activity values within a set of voxels in a region of interest (ROI) in the brain. In RSA, the activity pattern is interpreted as the representation of a certain condition within that ROI. This method can be used to test whether two conditions or stimuli elicit different activity patterns within a region. If two conditions evoke significantly different activity patterns, one can conclude that the region encodes something about the difference between the two conditions. The difference between the activity patterns for each pair of conditions is shown in the representational dissimilarity matrix (RDM). The most common form of RDM is a square matrix in 2D, where both rows and columns are indexed by the experimental conditions. In this type of RDM, each value indicates the dissimilarity between the activity patterns associated with a pair of conditions. Several measures of dissimilarity can be used (e.g., correlation, Euclidean distance, Mahalanobis distance). The diagonal entries represent the comparison between the same conditions and are equal to zero. A more compact format for an RDM is the lower-triangular vector, obtained by removing the redundant upper entries from the square 2D matrix. In RSA, RDMs for each region of interest (or ROI RDMs) are constructed and statistically compared to various model RDMs. Model RDMs can be derived from conceptual (or categorical) and computational models, or from behavioural data that capture the distinction between the conditions. First level RDMs are used to represent the distinction between each pair of conditions or stimuli. Second level RDMs can be used to represent the difference between multiple brain region or model RDMs.

In this work, RSA was applied to examine the extent to which the distinction between Task (paced, unpaced) and Movement Type (intermittent, continuous) were encoded in the functional activity of the cerebellum. To this aim, five model RDMs were constructed and tested on the brain functional data: two categorical models representing the distinction between the levels for Task (paced, unpaced) and Movement Type (intermittent, continuous), taken in isolation; three behavioural models, of which two were constructed out of the EMG signal recorded simultaneously with fMRI acquisition, EMG-based mean ITI and median EMG amplitude and one was built out of the lag-1 autocorrelation function (ACF) measured during the behavioural session (see **Figure 6.5**).



Mean ITI

0.00	0.23	0.26	0.22
0.23	0.00	0.28	0.22
0.26	0.28	0.00	0.22
0.22	0.22	0.22	0.00

EMG Amplitude

0.00	0.20	0.28	0.25
0.20	0.00	0.25	0.26
0.28	0.25	0.00	0.20
0.25	0.26	0.20	0.00

Lag-1 ACF

0.00	0.33	0.36	0.35
0.33	0.00	0.32	0.30
0.36	0.32	0.00	0.32
0.35	0.30	0.32	0.00

Figure 6.5 *Model RDMs used in RSA analysis. From left to right, categorical models for Task and Movement Type, and the behavioural models constructed out of the EMG-based mean ITI, the median EMG amplitude and the lag-1 autocorrelation function (ACF), averaged across all participants. The values shown for the behavioural models correspond to the Euclidean distances calculated for each pair of conditions. Smaller distance values indicate more similar conditions.*

The categorical models allow testing whether each experimental factor, taken in isolation, was encoded in the functional activity of a given brain region. As discussed in the introduction, in case the distinction between movement types is encoded in the activity pattern of a ROI, it is interesting to ask whether it is the motor demands of the task that are represented, or some other processing specific to the achievement of the timing goal. Each hypothesis was tested, by calculating the dissimilarity between each ROI RDM and the relevant behavioural model RDM. The hypothesis of a motor representation was tested with the behavioural RDMs based on mean ITI and (median) EMG amplitude: the RDM based on mean ITI should capture any differences in tapping rate across conditions; the RDM based on EMG amplitude should capture any differences in muscle's activation, expected for different movement types (i.e., intermittent and continuous movements). The hypothesis for the cerebellum to carry out processing specific to the sensorimotor synchronisation was tested with the behavioural model based on the lag-1 ACF (see result **Section 6.5.1**). One thing to notice, however, is that the data used to build the model for lag-1 ACF was not acquired simultaneously with fMRI acquisition, but during the behavioural session. In principle, this could have introduced a disadvantage, because the data collected in the behavioural session does not necessarily capture task performance in the functional session. However, a model RDM built out of data collected on a separate session has been used successfully before (Ejaz et al., 2015).

6.3.5.2.1 Region of interest (ROI) definition. Three macroanatomical cerebellar regions, bilateral lobules V, VI and VIII, were selected as ROIs. These lobules are consistently activated in finger-tapping tasks (Witt, Laird & Meyerand, 2008; Stoodley & Schmahmann, 2009) and have reciprocal connections with the primary motor cortex (Kelly & Strick, 2003). Moreover, lobule VI was suggested to be involved in the processing of the temporal aspects of an auditory stimulus (Spencer & Ivry, 2012). Given the strong lateralisation of these cerebellar lobules, with right areas preferentially coupled with left motor cortical areas, only ROI ipsilateral to the moving hand were considered. Notice also that these lobules showed some functional activation in all task conditions, detected with univariate analysis (*task* > *rest*, at an uncorrected threshold of $p < 0.001$, **Figure 6.8**). The left primary auditory cortex (A1) was selected as an additional ROI; A1 was chosen as a positive control, to show that the distinction for Task was represented at least in a region that processes auditory stimuli.

All ROIs in the cerebellum were defined with the probabilistic SUIT atlas of the cerebellum (Diedrichsen et al., 2006), by thresholding the probabilistic map for each ROI (≥ 0.6), binarizing it, and projecting it back into the individual functional space. The ROI for the primary auditory cortex was defined using the Jülich histological atlas (primary auditory cortex TE1.0), following a similar procedure as done for the cerebellum.

6.3.5.2.2 Representational dissimilarity matrices (RDMs). RDMs were calculated for each ROI, participant and scanning session, from the regression coefficients (or beta estimates) and the residuals from the GLM analysis. First, the activity patterns given by the regression coefficients were pre-whitened using the GLM's residuals. The dissimilarity between activity patterns within each ROI was calculated for each pair of the 4 conditions using the cross-validated squared Mahalanobis, or 'crossnobis' distance (Nili et al., 2014). The distance was calculated for each possible pair of imaging runs, then averaged across all pairs of runs. As a result of the cross-validation, if two patterns are not statistically different from each other the expected value of the distance is zero. When the distance is larger than zero, than there is differentiation between conditions. Notice that the crossnobis distance is not a distance in the mathematical sense and it can take negative values.

6.3.5.2.3 Comparing ROI and model RDMs. Each ROI RDM was compared separately to all candidate model RDMs. The comparison was carried out with correlations between pairs of ROIs and candidate model RDMs (compareRefRDM2candRDMs function from RSA toolbox). The Kendall's τ-a was used as correlation coefficient, which is suitable when comparing real data with categorical models. Statistical inference on the correlation was performed with a one-sided Wilcoxon signed-rank across participants, against the null hypothesis of zero correlation ($p < 0.05$). False discovery rate (FDR) was used to correct for multiple comparisons across all candidate RDMs. The compareRefRDM2candRDMs function also calculates a ceiling estimate for each comparison, defined as the average correlation of the true model RDMs with the single-participant ROI RDM, given the variability across participants.

6.5 Results

6.5.1 Intermittent and continuous rhythmic movements

Longer pauses were executed at each tap (i.e., at full finger flexion) in intermittent movements (mean [SD] = 170 [77.3] ms), compared to continuous movements (mean [SD] = 111 [48.1] ms, $t_{(26)} = 5.130$, $p = 2.39*10^{-5}$, d = 0.987). In intermittent movements, longer pauses were made also at full finger extension (mean [SD] = 107 [58.9] ms), compared to continuous movements (mean [SD] = 78.9 [47.0] ms, $t_{(26)} = 2.668$, p = .013, d = 0.513). As shown in **Figure 6.6**, intermittent and continuous movements were associated with distinct position-velocity profiles, as in Torre and Balasubramaniam (2009).

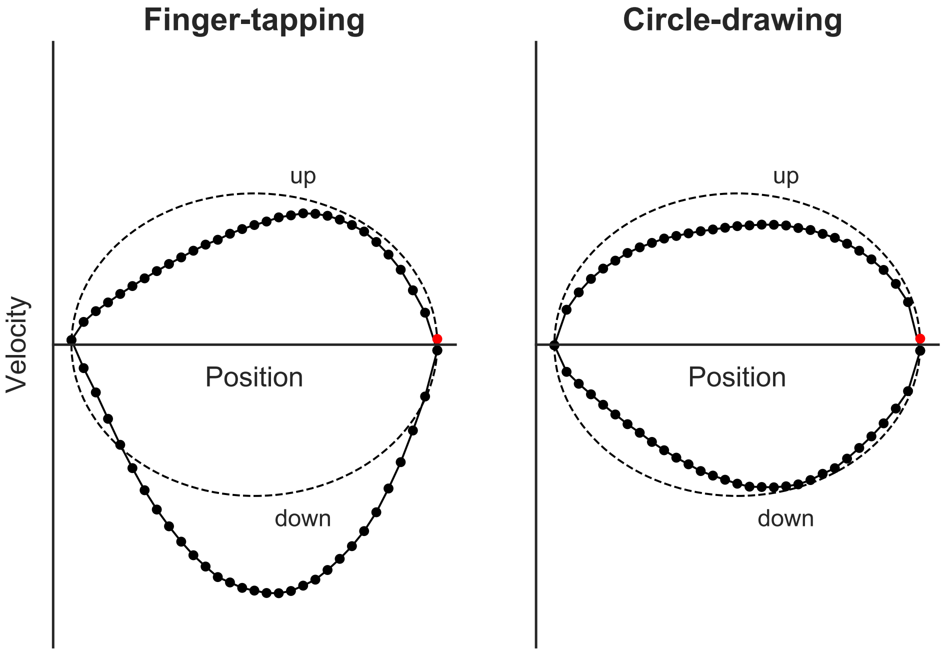


Figure 6.6 *Mean limit cycle averaged over 31 movement cycles and over all participants, for intermittent movements (left) and continuous movements (right). The figure shows mean position (x-axis) and velocity (y-axis) for an entire tapping cycle. Velocity and position values are in standard units. The red dot represents the occurrence of the metronome sound. The dashed circles represent harmonic movement with equal distribution of velocity across the upward and the downward phases.*

This distinction is reflected in a larger asymmetry in peak velocity for intermittent (mean [SD] = 27.6 [11.6]), compared to continuous movements (mean [SD] = 2.90 [9.34], $t_{(26)}$ = 11.126, p = 2.198*10 $^{-11}$, d = 2.141). The interaction for the lag-1 autocorrelation was also significant, $F_{(1,26)}$ = 7.371, p = .016, $\eta_G{}^2$ = 0.024 (see **Figure 6.7**).

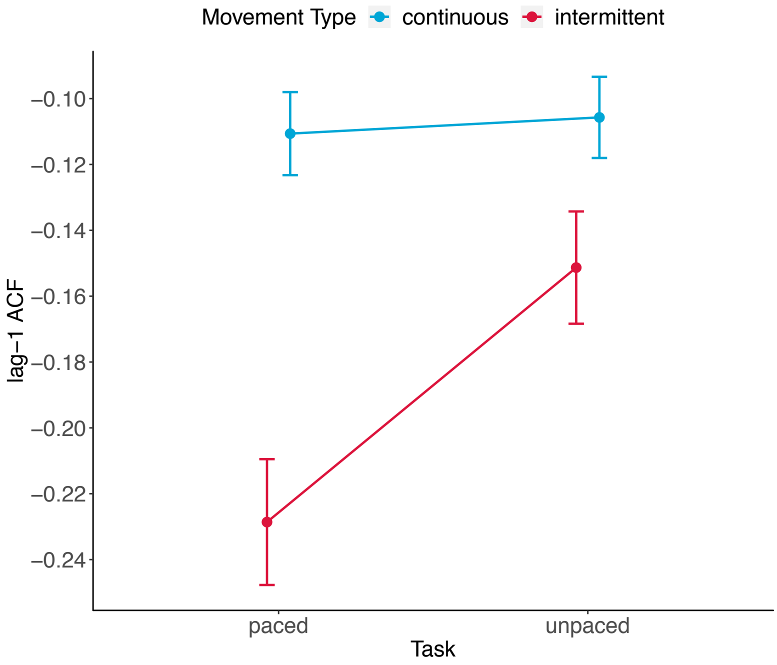


Figure 6.7 *Lag-1 autocorrelation function (ACF) for intermittent (red lines) and continuous (light blue line) movements, measured for the paced and the unpaced tasks. The lag-1 ACF is a measure of tap-to-tap error correction: larger negative values indicate a larger influence over each ITI at time N, from the ITI at time N-1. Error bars are 95% between-participants confidence intervals.*

In the paced task, larger negative values were observed in intermittent movements (mean [SD] = –0.229 [0.145]), compared to continuous movements (mean [SD] = –0.111 [0.130], $t_{(26)}$ = 5.38, p = 1.24*10^{-5}, d = 1.04). In the unpaced task, lag-1 ACF tended also to be larger for intermittent tapping (mean [SD] = –0.151 [0.096]), compared to continuous movements (mean [SD] = 0.106 [0.094]), $t_{(26)}$ = 2.46, p = .021, d = 0.47. The significance, however, did not survive Bonferroni correction for 3 comparisons. As shown in **Figure 6.7**, the difference between movement types was larger for the paced, compared to the unpaced task ($t_{(26)}$ = 2.72, p = .0116, d = 0.52).

6.5.2 Auditory-Motor Synchronization

The interaction between Task and Movement Type for the mean inter tap interval (ITI) was significant ($F_{(1,26)} = 27.0$, $p = 2.023*10^{-5}$, $\eta_G^2 = 0.08$, **Figure 6.8**).

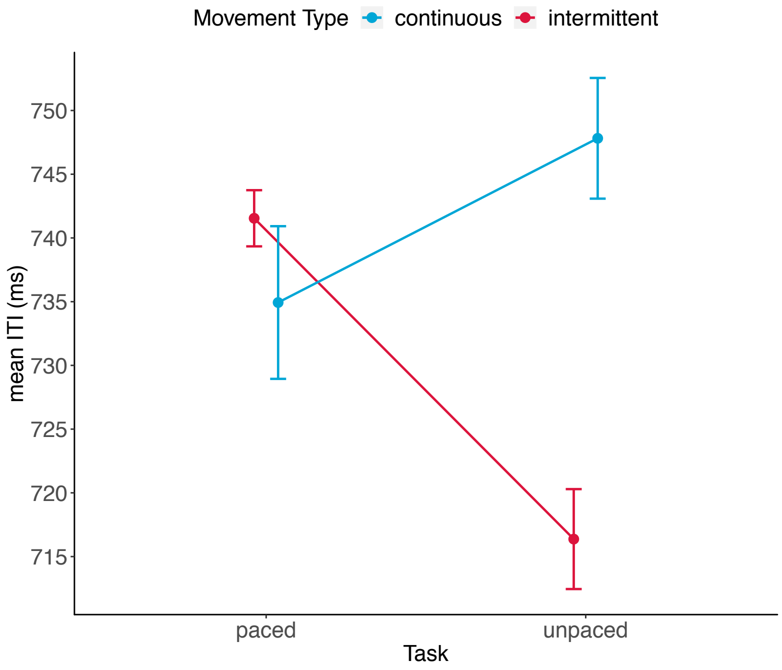


***Figure 6.8** Mean inter tap interval (ITI) for intermittent movements (red line) and continuous movements (light blue line), measured in the paced and the unpaced tasks. Error bars are 95% between-participants confidence intervals.*

In the continue task, mean ITI in intermittent movements (mean [SD] = 716 [45.5] ms) was shorter compared to continuous movements (mean [SD] = 748 [36.0] ms, t(26) = 5.60, $p = 6.913*10^{-6}$, d = 1.08). Mean ITI in the unpaced task for intermittent movements (mean [SD] = 716 [45.5]) was also shorter than mean ITI in the paced task (mean [SD] = 742 [16.7] ms, $t_{(26)} = 3.51$, p = 0.002 , d = 0.676). In the paced task, instead, intermittent movements, mean [SD] = 742 [16.7] ms, and continuous movements, mean [SD] = 735 [29.8] ms, were comparable ($t_{(26)} = 1.46$).

The coefficient of variation of ITI, instead, was comparable across conditions (all $F_{(1,26)} < 1.79$). Moreover, comparable negative asynchronies were observed in the paced task for intermittent, mean [SD] = –54.5 [76.5] ms, and continuous movements, mean [SD] = –66.7 [78.6] ms, ($t_{(26)} = 0.931$). Descriptive statistics for all behavioural measures are reported in **Table 6.1.**

Table 6.1 *Mean (and standard deviation) for the main behavioural measures for intermittent and continuous tapping, measured in the paced and the unpaced task.*

	Paced Task		**Unpaced** Task	
	Intermittent	**Continuous**	**Intermittent**	**Continuous**
Mean ITI (ms)	742 (16.7)	735 (29.8)	716 (45.5)	748 (36.0)
CoV ITI (%)	7.66 (3.08)	6.97 (1.85)	7.35 (2.85)	6.81 (3.48)
NA (ms)	– 54.5 (76.5)	– 66.7 (78.6)	-	-
lag-1 ACF	– 0.229 (0.145)	– 0.111 (0.130)	– 0.151 (0.096)	– 0.106 (0.094)
Peak velocity (cm/s)	25.5 (11.4)	17.6 (9.17)	24.9 (10.9)	17.6 (9.47)
Mean velocity (cm/s)	4.71 (1.97)	7.04 (3.98)	5.11 (2.34)	6.91 (3.98)

Movement Kinematics. The main effect of Movement Type for mean cycle velocity was significant ($F_{(1,26)} = 8.83$, $p = 0.0063$, $\eta_G^2 = 0.098$): mean movement velocity was higher for continuous movements (mean [SD] = 6.97 [3.97] cm/s), compared to intermittent movements (mean [SD] = 4.91 [2.13] cm/s). The interaction was also significant ($F_{(1,26)} = 9.69$, $p = 0.0045$, $\eta_G^2 = 0.002$), but this was explained by a higher mean velocity in the intermittent continuation (mean [SD] = 5.11 [2.34] cm/s), compared to intermittent synchronisation (mean [SD] = 4.71 [1.97] cm/s, $t_{(26)} = 2.75$, $p = 0.0108$, $d = 0.528$). By contrast, mean peak velocity was higher for intermittent movements (mean [SD] = 25.2 [11.1] cm/s), compared to continuous movements (mean [SD] = 17.6 [9.47] cm/s, $F_{(1,26)} = 35.56$, $p = 2.7081*10^{-6}$, $\eta_G^2 = 0.122$).

6.5.3 Behavioural session: Agreement between mean ITIs

The bias, quantified with the signed difference between the two measures of mean ITI is shown in **Figure 6.9**, plotted against the mean between the two measures (see Bland & Altman, 2010).

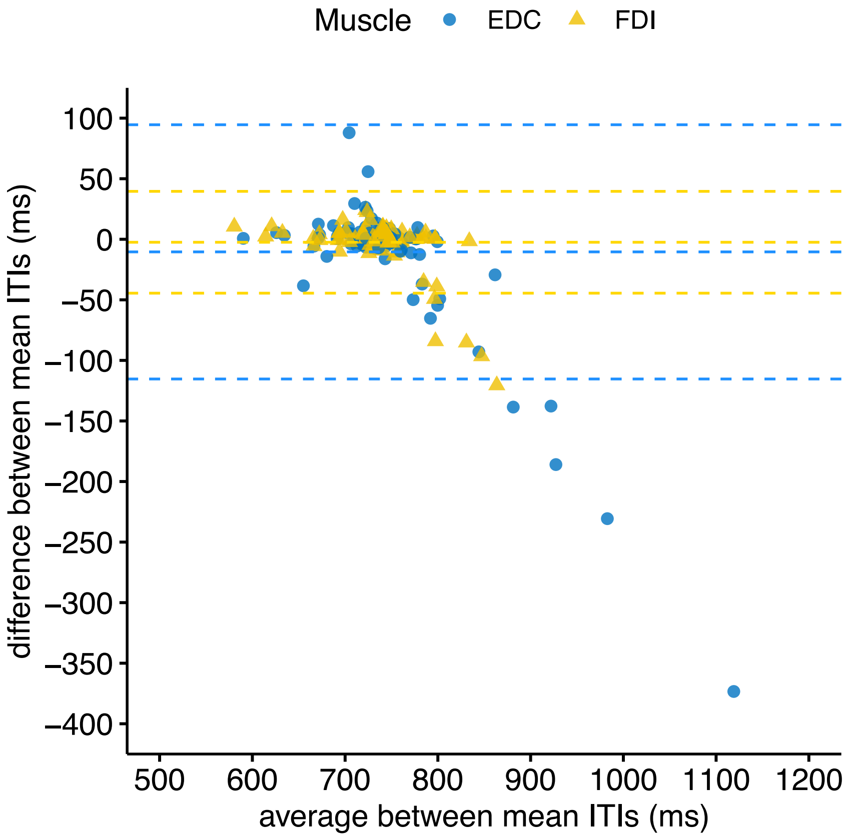


Figure 6.9
Average (x-axis) against the difference (y-axis) of the measures of mean ITI for FDI (in yellow) and EDC (in blue) muscles, for each participant and condition. Colour-coded horizontal lines represent mean (central) and 2 standard deviations from the mean (lateral).

Looking at **Figure 6.9** there seems to be some relation between the average and the difference of the two measures of mean ITI, with larger negative differences corresponding to larger average values, especially for the EDC muscle; this was due to a noisier EMG signal for some participants.

When the values for signed difference were compared across conditions, none of the effects considered reached significance (all $F_{(1,26)} < 3.74$). The values of mean signed difference were then averaged across conditions, separately for the FDI and the EDC muscles, then were entered in one-sample, two-tailed t-tests and compared against zero. Mean signed difference values for the FDI muscle, mean [SD] = –2.63 [12.0] ms, and the

EDC muscle, mean [SD] = –10.0 [32.7] ms, were both not different to zero (FDI: $t_{(26)}$ = –1.14, p = 0.263, d = 0.22; EDC: $t_{(26)}$ = 1.59, p = 0.124, d = 0.31).

The analysis on the absolute difference showed a significant interaction between Task and Muscle ($F_{(1,26)}$ = 6.86, p = 0.015, η_G^2 = 0.008), explained by larger (error) values, in the unpaced task, for the EDC muscle, mean [SD] = 43.4 [60.1] ms, compared to the FDI muscle, mean [SD] = 18.4 [16.3] ms ($t_{(26)}$ = 2.49, p = 0.020, d = 0.479). The interaction between Tapping and Muscle was also significant ($F_{(1,26)}$ = 4.74, p = 0.039, η_G^2 = 0.027). This effect was explained by larger values for continuous tapping, for the EDC muscle (mean [SD] = 43.9 [64.1] ms), compared to the FDI muscle (mean [SD] = 12.0 [4.81] ms, $t_{(26)}$ = 2.60, p = 0.015, d = 0.500). Of more concern, for the FDI muscle, the error was also significantly larger in intermittent (mean [SD] = 28.1 [29.2] ms), compared to continuous tapping (mean [SD] = 12.0 [4.81] ms), $t_{(26)}$ = 2.85, p = 0.008, d = 0.548.

Given that a smaller error was measured for the FDI and the EDC muscles, I decided to monitor the FDI muscle during the fMRI session. Even though the mean bias was comparable between FDI and EDC muscles, looking at **Figure 6.9** it is clear that the values for the EDC were spread more around zero, than the values for the FDI. Notice also that although the EDC muscle is more specific to movements of the index finger, the FDI gives a signal of larger amplitude, which makes it more robust to the artefacts from the scanner's magnetic field.

6.5.4 fMRI session: EMG-based mean ITI and EMG amplitude

The mean ITI calculated from the EMG signal recorded from the FDI muscle inside the scanner was comparable across conditions (all $F_{(1,11)} < 3.38$). When the median EMG amplitude was compared across conditions, the main effect of Movement Type was significant ($F_{(1,11)}$ = 6.70, p = 0.025, η_G^2 = 0.0007), with larger EMG amplitude for continuous movements (mean [SD] = 2.53 [3.10] mV), compared to intermittent movements (mean [SD] = 2.38 [2.97] mV).

6.5.5 Univariate Analysis

Functional activation observed for all 4 conditions (e.g., int*ermittent-paced* > *rest*, p < 0.001 uncorrected) covered similar areas in the cerebellum. The regions of activation rendered onto the SUIT atlas are shown in **Figure 6.10.**

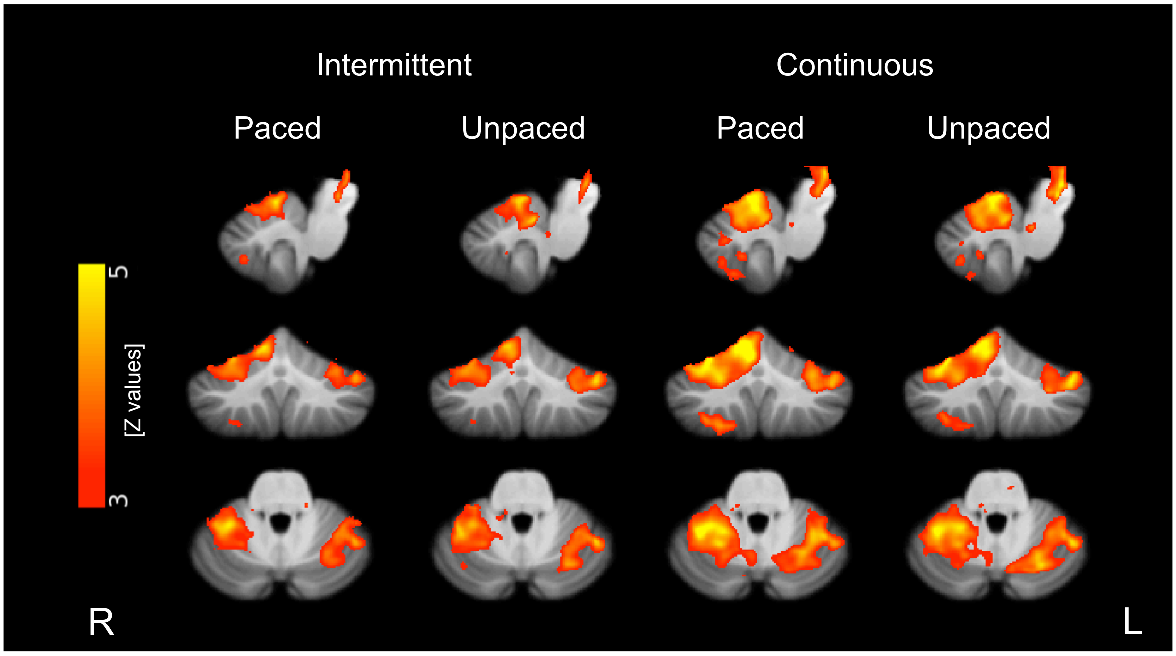


Figure 6.10 *Group t-maps of the evoked BOLD signal for each condition > rest, shown at an uncorrected threshold of p < 0.001 for intermittent and continuous movements measured with the paced and unpaced tasks. The results are presented on parasaggital (top, x = 10), coronal (middle y = –57), and axial (bottom, z = –28), slices of the SUIT template (Diedrichsen 2006). The figure is in the radiological convention.*

When the analysis was limited to the cerebellum, clusters of functional activity were observed only for the comparison *continuous > intermittent,* while no significant cluster was found for any of the other contrasts considered. Peaks of activation were found in the right lobules VI and VIIIb, as well as in the left lobule VI. The FEW-corrected critical cluster size was 180 voxels. The RESEL count was 1084.4 and FWHM was 5.9 x 5.3 x 5.6 mm. The results are reported in more detail in **Table 6.2** and the activation rendered onto the SUIT atlas is shown in **Figure 6.11**.

Table 6.2 *Random-effect analysis for contrast continuous > intermittent movements. Clusters are identified at an uncorrected t(11) > 4.02, p < .001 and corrected for cluster size over the volume of the cerebellum, based on cluster size (Worsley et al. 1996). The coordinates x, y, z for cluster peaks are in SUIT space (Diedrichsen et al., 2006). Labelling was done using the SUIT probabilistic atlas. Both the anatomical regions and the likelihood for activation to be in a certain region (in brackets) are reported in the table.*

Cluster level		**Voxel level**		**SUIT Atlas**	
P (FWE)	**equivk**	**P (FWE)**	**Z**	**x, y, z (mm)**	**Lobule**
0	9956	0.009	5.35	25, –48, –31	VI (10%) -V (4%)
0	1333	0.171	4.79	19, –59, –47	VIIIb (69%) - VIIIa (6%)
0	696	0.796	4.17	–39, –50, –27	VI (81%)
0.012	156	0.796	4.17	11, –16, 2	-

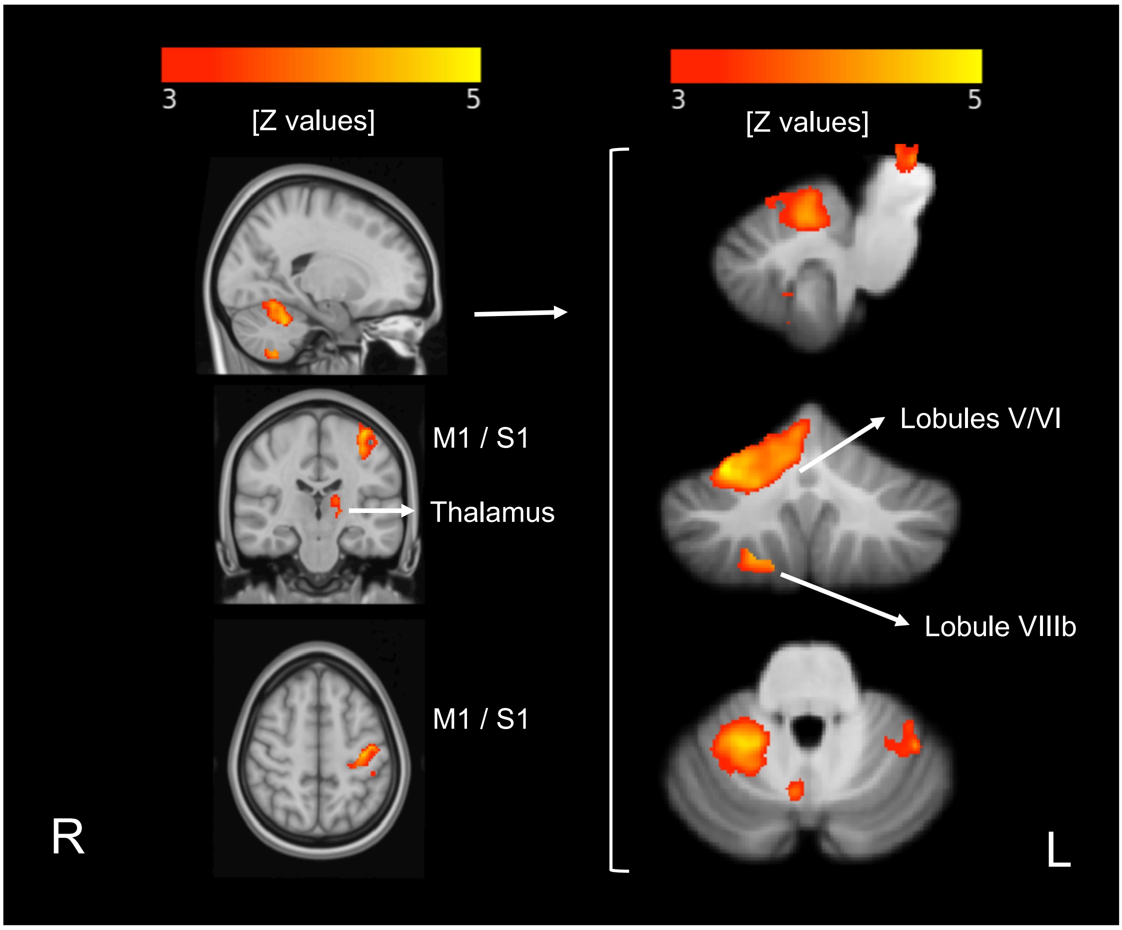


Figure 6.11 *Group Z-maps of the evoked BOLD signal for the contrasts continuous > intermittent for whole-brain (left side) and cerebellum and brainstem (right side), at an uncorrected threshold of* $t_{(11)} > 4.02$, $p < 0.001$. *Z-maps for the cerebellum were corrected for cluster size over the volume of the cerebellum. The results for the whole-brain are rendered on axial (z = 50), parasaggital (x = 20), and coronal (y = –22) slices of the MNI template, and for the cerebellum, on axial (z = –28), parasaggital (x = 10), and coronal (y = –57) slices of the SUIT template. The figure is in the radiological convention.*

When the analysis was extended to the rest of the brain (see **Figure 6.11**), cluster of activations were observed for the contrasts *paced* > *unpaced* and *continuous* > *intermittent*. The synchronise task, compared to the continue task activated more primary auditory cortex bilaterally and the right inferior parietal lobule. For this contrast the FEW-corrected critical cluster size was 52 voxels, the RESEL count was 5069.5 and FWHM was 7.6 x 7.8 x 7.6 mm. In addition to the cerebellum, continuous movements, compared to intermittent movements activated more the left thalamus, primary motor cortex, primary somatosensory cortex and premotor cortex. The FEW-corrected critical cluster size was 60 voxels, the RESEL count was 5212.4 and FWHM was 7.5 x 7.7 x 7.6 mm. Descriptive values for these contrasts are reported in **Table 6.3**.

Table 6.3 *Random-effect analysis for contrast paced > unpaced Task and continuous > intermittent Movement Type. Clusters are identified at an uncorrected t(11) > 4.02, p < 0.001. The coordinates x, y, z for cluster peaks are in Jülich Atlas or the Harvard-Oxford Subcortical Atlas (marked by a *). Labelling was done using either of these atlases. Both the anatomical regions and the likelihood for the activation to be in a certain region (in brackets) are reported in the table.*

	Cluster level		**Voxel level**		**Jülich Atlas and Harvard-Oxford Subcortical Atlas (*)**	
Contrast	**P (FWE)**	**equivk**	**P (FWE)**	**Z**	**x, y, z, (mm)**	**Anatomical region**
paced > unpaced	0	555	0.578	4.71	52, –6, 2	Primary auditory cortex TE1.0 (54%)
			0.9	4.52	58, –14, 8	Primary auditory cortex TE1.0 (31%)
			0.973	4.38	58, –28, 22	Inferior parietal lobule (50%)
	0	537	0.578	4.3	–50, –10, 2	Primary auditory cortex TE1.0 (58%)
			0.994	4.27	–52, –30, 10	Primary auditory cortex TE1.1 (25%)
			0.999	4.15	–58, –8, 6	Primary auditory cortex TE1.2 (30%)
continuous > intermittent	0	1225	0.029	5.21	30, –56, –22	Cerebellum
			0.196	4.84	6, –68, –32	-
			0.526	4.64	22, –48, –30	-
	0	1202	0.119	4.94	–24, –44, 58	Primary somatosensory cortex (29%); Superior parietal lobule 5L (28%)
			0.369	4.71	–38, –22, 64	Premotor cortex BA6 (64%)
			0.674	4.59	–36, –20, 52	Primary motor cortex BA4 (48%)
	0	144	0.923	4.5	12, –60, –56	Cerebellum
			0.992	4.29	20, –56, –56	-
	0,003	78	0.997	4.24	–16, –24, 0	Thalamus (97.6%)*
			0.454	3.81	–14, –20, 12	Thalamus (100%)*

6.5.6 Representational similarity analysis (RSA)

The ROI RDMs for each region of interest, based on the “crossnobis” are shown in **Figure 6.12**.

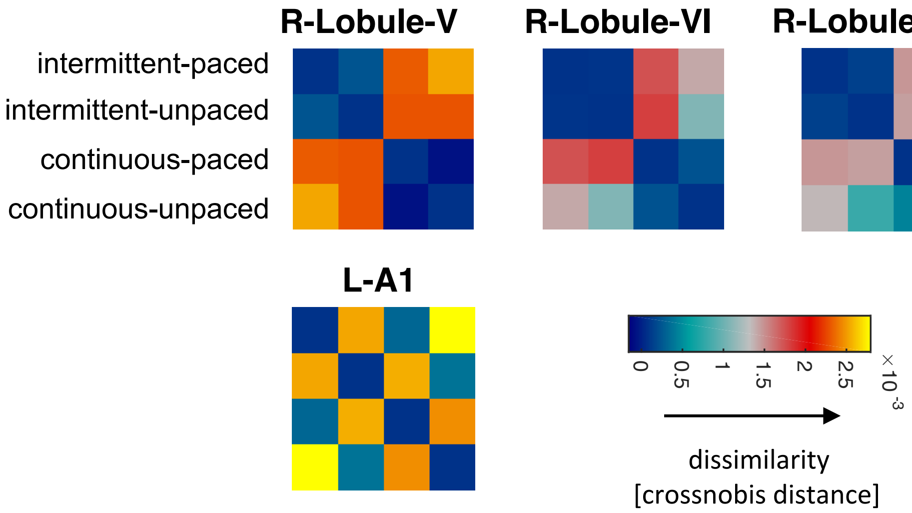


Figure 6.12 *Representational similarity matrices for right cerebellar lobules V, VI and VIII, left putamen and left primary auditory cortex (A1). The cell of the RDMs are indexed by the experimental conditions and show the cross-validated Mahalanobis distance. From top to bottom, left to right, the cell corresponds to conditions “intermittent-paced”, “intermittent-unpaced”, “continuous-paced” and “continuous-unpaced”. The closer the values to zero (blue-shaded cells), the more similar the activity patterns for the conditions.*

6.4.5.1 Comparing ROI and model RDMs

As expected, the ROI RDM for the left primary auditory cortex was significantly correlated only with the categorical model for Task ($p = 0.0005$). This model is likely capturing the presentation of metronome sounds that were played only in the paced task.

The ROI RDMs for all cerebellar lobules correlated both with categorical model for Movement Type (all $p < 0.0005$) and with the behavioural models based on median EMG amplitude (all $p < 0.0002$) and EMG-based mean ITI (all $p < 0.0027$, see **Figure 6.13 A, B and C**). For Lobule VI, none of the models reached ceiling (represented with grey shaded bars in **Figure 6.13 D**), indicating that there was still unexplained variance in the brain data. Instead, the correlations with the behavioural model on Lag-1 ACF (all $p > 0.0508$) and the categorical model of Task (all $p > 0.994$) never reached significance.

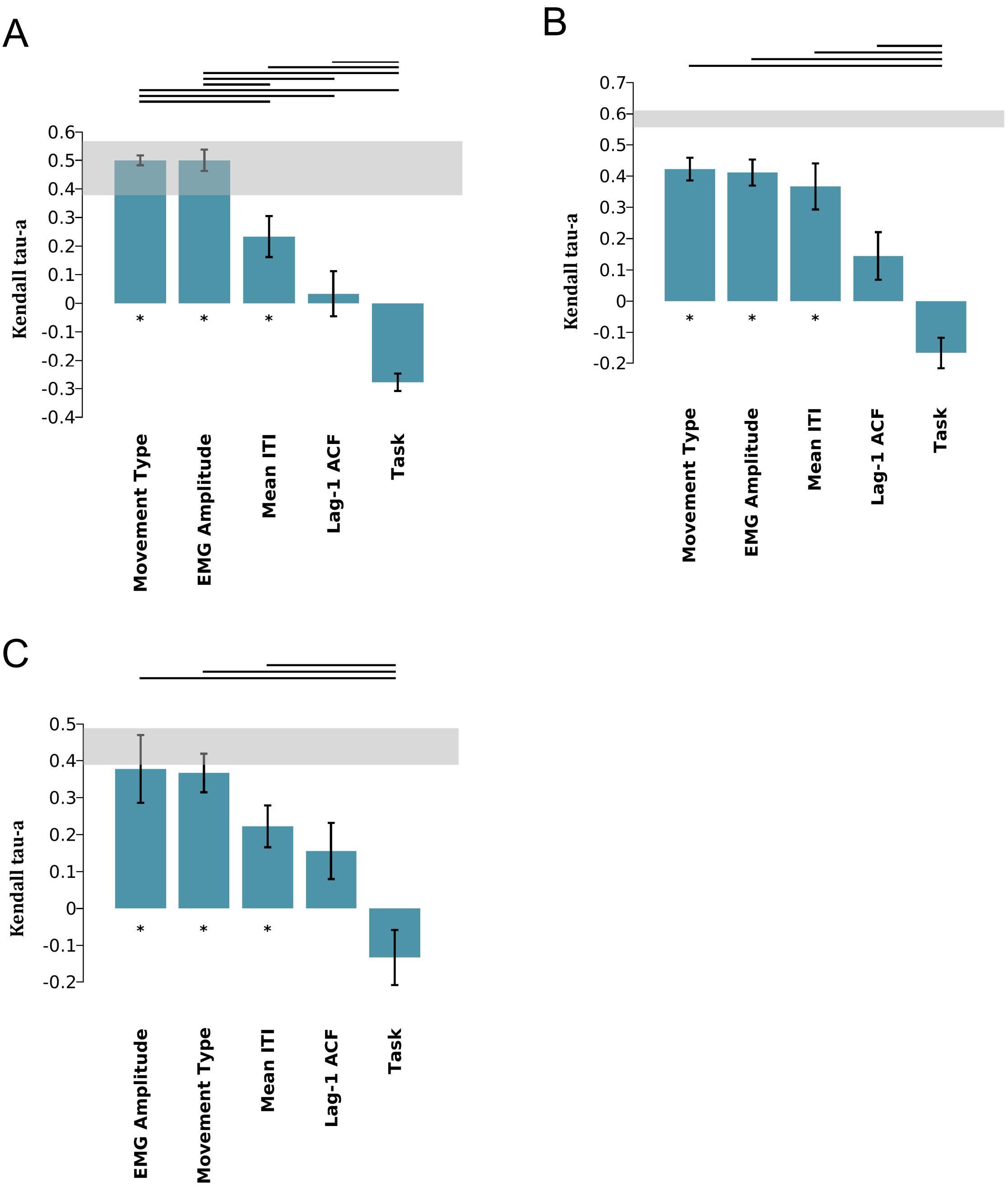


Figure 6.13 *This figure shows the correlation between each reference ROI RDM, for cerebellar lobule V (A), lobule VI (B), lobule VIII (C) and each of the competing model RDMs (i.e., Task, Movement Type, EMG amplitude, mean ITI, Lag-1 ACF). Stars indicate the models that significantly correlated with ROI RDMs. The horizontal lines indicate the significant pairwise comparisons ($p < 0.05$ with FDR correction). The grey transparent horizontal bars represent the noise ceiling estimated from the data. The upper and lower edges of this bar indicate the estimates for the bounds of the best possible model fit. Error bars indicate the standard error of the mean.*

6.6 Discussion

With this work I aimed to examine further the dissociation between intermittent and continuous rhythmic movements in the context of auditory-motor synchronization (Torre and Balasubramaniam, 2009). In order to study auditory-motor synchronization, intermittent and continuous movements were examined at different task requirements, with the paced and the unpaced version of the finger-tapping task. While the paced version required participants to synchronise their periodic finger movements (intermittent or continuous) with a metronome, the unpaced version of the task did not require auditory-motor synchronisation and the rhythm had to be internally generated. According to plan, intermittent and continuous movements showed features compatible with the movement types examined by Torre and Balasubramaniam (2009): 1) a more prominent asymmetry in the position-velocity profile for intermittent, compared to continuous movements; 2) a more negative lag-1 autocorrelation function (ACF) for intermittent, compared to continuous movements; with a larger difference between movement types for the paced, compared to the unpaced movements. This second result can be interpreted as a stronger cycle-to-cycle error correction for intermittent, compared to continuous movements, especially when a pacing auditory stimulus is presented.

Synchronisation performance as estimated by the variability in the inter-tap-interval (Spencer et al., 2003) was comparable across conditions. This indicated that there was no clear advantage for one movement type over the other, or from the presentation of an auditory cue. The mean inter-tap-interval (ITI) differed across conditions, with shorter intervals measured in the unpaced task for intermittent movements, compared to continuous movements. This was likely due to the fact that the preferred movement rate, in the absence of a pacing stimulus, was slower when drawing circles (continuous movements), then when executing vertical taps (intermittent movements). Notice however that this difference was not observed in the fMRI session, possibly due to the choice of shorter trials. All in all, the variable that better characterised the behavioural differences across task conditions was the lag-1 ACF.

In the functional MRI session, as expected, ipsilateral cerebellar lobules V, VI and VIII were found to be activated by all conditions, compared to rest. Besides, continuous movements, compared to intermittent movements activated several motor regions in the brain to a greater extent. Cluster of activation were found in bilateral lobules VI and right lobule VIIIb, left thalamus, left primary sensory and motor cortices, and left premotor cortex. The result of the cerebellum being more activated by continuous, compared to intermittent movements is opposite to what was found by Spencer and colleagues (2007). However, as the authors pointed out, the observed difference in activation could have been introduced by a difference in the motor component of the task. In accordance with this interpretation, in their work continuous movements were slower than intermittent movements. In the present experiment, the larger BOLD response found with classic analysis, for continuous, compared to intermittent movements most likely reflected a difference in the motor component of the two movement types. This conclusion is supported by the results from RSA. In RSA, the categorical model for Movement type, performed equally well as the behavioural model based on EMG amplitude (for all cerebellar lobules), and the model based on mean ITI (for lobules VI and VIII). This suggests that the lobules were likely to represent motor the motor demands of the task.

The hypothesis of a difference between the four conditions in terms of task requirements was tested with the behavioural model for lag-1 ACF. Lag-1 ACF, in fact, was shown to differ across conditions as reported also by Torre and Balasubramaniam (2009). The lag-1 ACF model did not correlate with any cerebellar RDMs. Even though this model was the only one based on data collected during the behavioural session and this could have introduced a disadvantage, building a model out of the data from a different session has been successful before (e.g., Ejaz et al., 2015). Importantly, of all measures of auditory-motor synchronisation performance, lag-1 ACF was the only measure that was shown to vary meaningfully across tasks and that clearly distinguished intermittent paced movements from all other conditions. Cycle-to-cycle movement variability, which was central to the study of cerebellar ataxia, instead was similar between conditions.

6.7 Conclusion

The research presented in this chapter focused on the role of the cerebellum in auditory-motor synchronisation, which can be described as the ability to move a limb, bringing it periodically to a spatial location, in some temporal relation with an external auditory stimulus. This ability is at the basis of complex behaviours like music production and dance, and has been studied with the finger-tapping task. In the context of auditory-motor synchronisation, a dissociation between intermittent and continuous rhythmic movements has been proposed (Torre & Balasubramaniam, 2009; Zelaznick et al, 2000; 2002; Spencer et al., 2003) and the cerebellum has been suggested to play a role in this dissociation (Spencer et al., 2003; Spencer et al., 2007). The prediction from these studies is that the cerebellum is specifically involved in temporally constrained intermittent movements. Previous studies have examined the neural basis with intermittent and continuous movements with functional MRI (Schaal et al., 2004; Spencer et al., 2007), but their results are confounded.

The experiment presented in this chapter was an attempt to further examine intermittent and continuous movements in the context of auditory-motor synchronisation and to overcome confounds present in previous studies. This was achieved using similar task requirements for the intermittent and continuous tasks (unlike in Schaal et al., 2004) and monitoring motor activation during the functional MRI session (see Spencer et al., 2007). Motor activation was monitored measuring EMG activity inside the scanner, simultaneously with fMRI acquisition. As a further strength of the work presented, RSA was employed to test the hypotheses for a cerebellar representation of processing specific to the achievement of the timing goal and a representation of the motor demands of the task. These hypotheses were expressed with behavioural models, which were tested against the activity patterns measured in the cerebellum.

Continuous, circular movements of the finger activated the cerebellum (bilateral lobules V/VI and right lobule VIII) more than intermittent, vertical movements. Moreover, this activation was more likely to reflect differences in the motor demands of the task (e.g., movement speed), rather than processing specific to the achievement of the timing goal (e.g., cycle-to-cycle error correction). In conclusion, with RSA I did not find a preferential cerebellar involvement in intermittent movements, compared to continuous movement, studied with the auditory-motor synchronisation task.

As an important limitation of this work, a more systematic characterisation of what constitutes the “processing specific to the auditory-motor synchronisation” is required to progress on this topic. Even though many measurements were taken of synchronisation performance, only the lag-1 ACF was shown to differ meaningfully across conditions. It is possible that the task adopted was not suitable for bringing to the surface behavioural and functional differences specific to the ability for auditory-motor synchronisation. As a second possibility, the hypothesis of temporal processing as required for auditory-motor synchronisation may be too loosely defined to be addressed with functional MRI and would require a more systematic characterisation to provide testable hypothesis of brain function. Despite the limitation outlined above, the advancements of this study were monitoring muscle activation during the functional session, as a way to gauge tasks’ motor demands, and using behavioural and physiological data, to directly test hypotheses of brain functioning.

Chapter 7. General Discussion

The experimental work presented in this thesis focused on the topics of timing and auditory-motor synchronization, abilities that are thought to form the basis of complex behaviours like music perception and production, and dance, but also speech and motor execution more broadly (for a review, Buhusi and Meck, 2005).

This concluding chapter includes a summary of all research questions addressed during my PhD and was written with the aim to describe the progression that led from the first experiment to the last. This chapter was divided into two main sections that parallel the work on time perception (work presented in **Chapter 4**) and the work on auditory-motor synchronisation (**Chapter 5** and **Chapter 6)**. What follows is an attempt to provide an answer to each question addressed, restating how conclusions are supported by the results, and are integrated in the relevant existing body of knowledge. While doing this, an effort has been made to underline any limitations, as well as any implications for future studies. Each section concludes with recommendations for future work in the relevant area of study.

7.1 Effect of a regular context on duration perception

7.1.1 Results summary

The first part of my PhD was spent examining the ability to make temporal judgments in humans, focusing on the effect of a temporally regular auditory context on duration perception. More specifically, I examined whether a regular compared to a non-regular context can influence duration perception, measured with a 2-interval forced choice (2-IFC) perceptual judgment task.

This study aimed at replicating the work of Barnes and Jones (2000) who showed that listeners were more accurate in judging the duration of intervals that were equal in length to the intervals presented in a regular context, compared to shorter or longer intervals. The authors interpreted this result by positing that a regular context can systematically influence the perceived duration of single auditory events, embedded in this context. Their work was influential and formed the basis of the dynamic attention theory (DAT). According to DAT, attention oscillates in time and can be entrained by presenting a regular sequence of sounds. As a result of this entrainment of attentional resources with the ongoing auditory periodicity, the processing of sounds in phase with this rhythm is facilitated.

With my experiments I showed that duration discrimination of two intervals presented in a sequence can be influenced by an auditory context, since temporal discrimination improved when a regular, compared to a non-regular context was provided. However, duration discrimination measured either with the just noticeable difference (JND) or with the point of subjective equality (PSE) was not modulated by the duration of the reference interval, as predicted by DAT. According to my speculation, this divergence in the results stemmed from differences in the methods used to quantify discrimination performance and from the confounding factor of the “session-range” (or “central tendency”) effect introduced by the range of reference intervals included in the experimental blocks, in the work of Barnes and Jones (2000). This effect arises when the estimated duration of an interval is biased toward the average of the intervals that proceeded.

Previous studies, in fact, have shown that when making temporal judgements in an uncertain context, humans rely on the temporal context generated over the course of an experiment (Jazayeri & Shadlen, 2010; Cicchini et al., 2012). Participants tend to gravitate towards the mean of the distribution from which the intervals are extracted, overestimating the duration of shorter intervals and underestimating the duration of longer intervals. Furthermore, the influence of prior experience on perceptual judgments is related to the degree of uncertainty in the response (Cicchini et al., 2012). This “central tendency” effect has been effectively explained within a Bayesian framework (Jazayeri & Shadlen, 2010; 2015). A Bayesian model is a generative model that combines prior expectations about a stimulus with current sensory evidence (i.e., the likelihood of the sensory evidence, given the stimulus) to compute the percept (i.e., the posterior probability of the stimulus).

7.1.2 Limitations

Time is an evasive concept that lacks tangible physical properties, which make time perception harder to investigate, compared to other more physical properties like colour, pitch, or smell, to name a few. Therefore, when studying temporal judgements it is especially important to evaluate construct validity, the degree to which a test actually measures what it claims to be measuring. For example, slightly different methods for measuring duration perception (i.e., temporal production or reproduction, verbal estimation, and time discrimination) can give substantially different results (Grondin, 2008; Zakay, 1990).

Researchers studying temporal perception have to overcome several limitations. First, temporal judgments are subject to temporal distortions (e.g., Horr & Di Luca, 2015; Thomas & Brown, 1974; Wearden et al., 2007; Buffardi, 1971; Adams, 1977; Rammsayer & Lima, 1991; Rammsayer & Leutner, 1996). Second, it is possible that the methods used to study time perception are actually measuring changes in decisional criteria, rather than time estimation (Solomon et al., 2012; Yarrow et al., 2015). Third, even when an experiment is carefully designed to study time perception, its ecological validity is still in question, because it is not assured that the timing ability under investigation is actually carried out outside the laboratory context. These limitations are tightly linked: the degree of uncertainty in a perceptual system when processing time determines how robust the measures of temporal judgments will be. The more the uncertainty in the judgment, the more the system will rely on other strategies, to accomplish the temporal judgment task. As a consequence of this, the time estimate provided will strongly dependent on the characteristic of the task itself.

7.1.3 Suggestions for future studies

The work presented in **Chapter 4** examined the ability to perceive the duration of an auditory event, or the ability to estimate how long an event lasted. Duration perception has been studied extensively (see Rhodes, 2018 for a review). However, as suggested by Rhodes in his review (2018), in order to build “a unified model of time perception”, researchers working in this field should shift their attention towards “perceived event timing”, the ability to estimate when an event is expected to occur in the world. From a theoretical perspective, measuring the duration and measuring the onset in time of an event differ only in the reference adopted for the measurement, rather than in the stimuli per se. For example, duration perception is typically studied with intervals delimited by a pair of stimuli, indicating an onset and an offset (although filled intervals have also been used, e.g., Thomas & Brown, 1974). Similarly, in event timing tasks participants are required to estimate when a stimulus is presented, relative to a similar preceding stimulus. Therefore it is important to understand these tasks are solved in a different way.

Future experiments should strive to provide a synthesis of duration perception measured with different methods, as well as of duration perception and event timing (see Rhodes, 2018). A unified theory may take the form of a testable probabilistic model, which would facilitate integration of several pieces of evidence (for example, see Tanenbaum et al., 2006). The Bayesian probabilistic approach seems to provide the best mean to reach this goal and has already been applied successfully to both duration perception (Jazayeri & Shadlen, 2010; Hartcher-O'Brien et al., 2014; Miyazaki et al., 2005; Shi et al., 2013) and event timing (Di Luca & Rhodes, 2016). More broadly, a unified model should integrate both temporal processing with learning and decision-making processes. This would allow assigning a weight (or probability) to each process and would help identify those tasks (if any) that are naturally solved through the processing of temporal information.

7.2 Auditory-motor synchronisation: Dissociation between intermittent and continuous movements

In order to tap in anticipation to the sounds of a regular sequence (for example, when a metronome is playing), a listener first needs to form temporal expectations that allows him/her to anticipate both the timing of future sounds and the timing of taps, relative to these sounds. Therefore, effective anticipatory auditory-motor synchronization behaviour, which distinguishes human finger-tapping from that of non-human primates (Zarco et al., 2009), has been suggested to rely on temporal processing and on the detection of temporal regularities (Spencer et al., 2003; Spencer et al., 2005). As a result of this, perceptual timing and auditory-motor synchronization are interrelated areas of study.

Despite these considerations, my experiments on duration perception and on auditory-motor synchronization are not directly connected. I could have easily spent my entire PhD working on time perception, with the advantage of a better narrative cohesion. Instead, I moved onto motor research and used the second part of my PhD to study auditory-motor synchronization, driven also by curiosity in the methods and techniques available at the Hand Lab (i.e., transcranial magnetic stimulation – TMS, motion-tracking, surface electromyography – EMG).

In the second part of my PhD, I examined the role of the cerebellum in intermittent and continuous rhythmic movements. A dissociation between intermittent and continuous rhythmic movements was suggested, after observing increased finger-tapping variability in patients with cerebellar ataxia. Importantly, an increase in movement variability was observed for intermittent, but not for continuous movements, studied with the synchronise-continue task (Irvy et al., 2002; Spencer et al., 2003). Furthermore, this difficulty in the synchronise-continue task did not seem to result simply from a motor deficit, but to depend on a difficulty in timing the movements (Spencer et al., 2005). This dissociation has been explained in terms of different control mechanisms: Intermittent movements are thought to rely on the setting of a timing goal for correct execution. According to this view, in the absence of movement the brain cannot rely on updating proprioceptive and motor signals, to keep track of the passage of time (event timing). Instead, continuous movements are thought to emerge from the setting on non-temporal parameters like movement speed and acceleration for correct execution (emergent timing; Spencer et al., 2005). The role of the cerebellum in the dissociation between intermittent and continuous movements was examined using single-pulse TMS (work presented in **Chapter 5**) and functional magnetic resonance imaging (fMRI; **Chapter 6**).

7.2.1 TMS experiment

7.2.1.1 Results summary

I decided to use single-pulse TMS to examine whether I could increase finger-tapping variability, by applying TMS over the cerebellar hemisphere ipsilateral to the moving hand, compared to when stimulating a location on the contralateral cerebellar hemisphere. In doing this, I relied on evidence for a strong lateralization of function in the motor system, where each effector is predominantly controlled by the contralateral cerebral cortex and the ipsilateral cerebellum. A study addressing the same question with the use of repetitive TMS delivered over the cerebellum, showed a hemispheric-specific effect of interference in finger-tapping synchronisation with auditory stimuli (Del Olmo et al., 2007). In my study, I used TMS to examine also the dissociation between intermittent and continuous movements, expecting to observe a stronger increase in tapping variability for intermittent, compared to continuous movements.

Contrary to expectations, single-pulse TMS did not affect finger-tapping performance as expected – i.e., in a hemisphere-specific way. With the first experiment I observed a TMS-specific global increase in finger-tapping variability that was larger for intermittent, compared to continuous tapping. However, this effect was not hemisphere-specific and was not replicated in the second experiment. In both experiments I observed a short-lasting effect of TMS on the taps around the time of stimulation. However, once again these effects were not hemisphere-specific and were also qualitatively different in the two experiments. Given that TMS over the contralateral hemisphere was chosen as a control condition, the TMS-specific effects are likely to result from a combination of confounding factors, such as stimulation of peripheral nerves and of neck and shoulder muscles, abrupt discomfort and a non-habituating startle-like effect, all known to affect movement kinematics (Fisher et al., 2009).

7.2.1.2 Limitations and suggestions for future studies

The main limitation of this study lies in the technique: cerebellar TMS. As pointed out in **Chapter 3**, a consensus on the effectiveness of cerebellar TMS is still to be reached (Fisher et al., 2009).

Among the limitations, cerebellar TMS can simultaneously activate several structures in the brainstem, making it difficult to localise the effect to an isolated region. This is even more the case, when using the large double-cone coil that can reach deeper brain regions only at the cost of reduced focality (Hardwick et al., 2014). Furthermore, the effect of magnetic stimulation on the cerebellum is also not directly measurable; this makes it harder to agree on a standard practice for setting threshold for stimulation (for example, notice that I failed to observe brainstem-related MEPs for most of the participants tested). Another concern is that the effect of TMS is not confined to the brain, because TMS can stimulate also afferent fibres in the posterior neck and can influence the excitability of the corticospinal tract (Fisher et al., 2009). All these confounding factors should induce a degree of caution, when interpreting the results, enough to discourage final conclusions (for example, see Xu-Wilson et al., 2011).

On a final note, the reliability of the positive results reported in the literature (e.g., Del Olmo, 2009) cannot be assessed, without first addressing the publication bias, because the number of studies that used cerebellar TMS with a similar purpose, but failed to show a significant result is hard to estimate (Rothstein et al., 2005). Researchers interested in cerebellar TMS should focus on validating the technique, rather than testing hypotheses of brain functioning; they should also strive to provide guidelines for standard practice.

7.2.2 fMRI experiment

7.2.2.1 Results summary

Functional MRI has been used with the aim to examine the neural basis for a dissociation between intermittent and continuous movement. Previous studies predicted a larger activation in cerebellar lobules ipsilateral to the moving hand, for intermittent, compared to continuous movements (Spencer et al., 2003; 2007). However, results interpretation was confounded by difference in the motor component of the task (see Spencer et al., 2007): functional activation in motor regions is known to correlate with parameters of movement (Deiber et al., 1999, Jäncke et al., 1999, Sadato et al., 1997), therefore it is not clear to what extent a difference in activation between intermittent and continuous movements is to be attributed to differences in motor execution, rather than differences in temporal processing.

In the experiment reported in **Chapter 6**, intermittent movements (i.e., finger-tapping) and continuous movements (i.e., circle drawing) were very different in terms of motor kinematics. However, the approach adopted consisted in allowing for motor differences across tasks, as long as these could be quantified. More specifically, the motor confound was addressed by: 1) monitoring muscle activity simultaneously with fMRI acquisition and quantifying differences both in motor kinematics and in synchronization performance; 2) using these measures as predictors in representational similarity analysis (RSA), to test the hypothesis for a cerebellar representation of different motor demands and different processing required for the achievement of the timing goal. All task conditions were shown to activate the hand motor region in the cerebellum (i.e., lobules V/VI and lobule VIII). Activation in these lobules was also stronger for continuous, compared to intermittent movements. Based on the evidence available, right lobules V, VI and VIII were selected as regions of interest for RSA (Witt et al., 2008; Stoodley & Schmahmann, 2009). The representational dissimilarity matrices (RDMs) for all these lobules were found to correlate with the model RDM that reflected differences in the motor demands of the task (Mean ITI captured movement rate, EMG amplitude, the degree of muscle activation). Instead, cerebellar RDMs were not correlated with the model RDM based on lag-1 ACF, which was chosen to represent differences in the achievement of the timing goal. The results did not provide evidence to support the hypothesis of different temporal processing for intermittent, compared to continuous rhythmic movements carried out by the cerebellum.

7.2.2.2 Limitations and suggestions for future studies

Intermittent and continuous movements imply different movement kinematics. When studying functional activation in response to a motor task, with the intention to study non-motor processing carried out in a motor region (e.g., the cerebellum), one has to account for differences in motor demands of the task, to start with. The proposed way to address this issue is to characterise any motor differences with quantifiable measures and directly testing the hypotheses for a representation of motor demands and the achievement of a timing goal. Despite the problem of motor confounds being introduced as the biggest challenge, the main limitation of the study was likely the lack of a model that effectively captured the “processing specific to the achievement of a timing goal”. Even though the lag-1 ACF was shown to meaningfully vary across task conditions and to capture an important difference between intermittent and continuous rhythmic movements (Consistent with Torre & Balasubramaniam, 2009; Delignières et al. 2008; Lemoine and Delignières 2009; Torre and Delignières 2008), the model based on lag-1 ACF is unlikely to fully capture what is defined as "processing specific to the achievement of a timing goal", because this measure captures only cycle-to-cycle error correction, but it is not a measure of temporal processing. The hypothesis of temporal processing may be too loosely defined to be addressed with functional MRI. My speculation is that the study of temporal processing is important, but the discourse around time, at present, may be better carried out at the level of the mind, rather than the brain. In order to transition from mind to brain, a more systematic characterisation is required.

8. References

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9. List of Tables

10. List of Figures