Action, time, and uncertainty: two types of temporal uncertainty in cognitive motor control

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I, Friederike Schüür, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

Time is a fundamental dimension of cognition and motor control. Preparation for imperative events, choosing the appropriate time to act if there are no external triggers, or deciding between action alternatives if their outcome depends on accurate timing, requires accurate estimates of time. Typically, the accuracy of such estimates is limited and we experience temporal uncertainty. I here distinguish between two types of temporal uncertainty: (a) *external* temporal uncertainty (ETU), which arises when the timing of imperative events is variable and (b) *internal* temporal uncertainty (ITU), arises as a consequence of “noisy” internal clocks. I present behavioural and neurophysiological studies on the effects of ETU and ITU on human cognitive motor control. A series of experiments first addressed how participants prepare for action in the face of ETU and ITU. Second, I explored the interaction between ETU, ITU, and uncertainty about the *type* of motor response (*event uncertainty*). Using transcranial magnetic stimulation (TMS), two experiments probed the neurophysiology of preparation for action under condition of ETU. One experiment aimed at offering a functional account of changes in cortico-spinal excitability (CSE), a measure of motor preparation, prior to imperative events by manipulating ETU. In a second experiment I then further explored the functional role of $GABA_A$ and $GABA_B$ receptor-dependent intracortical inhibitory circuits for action preparation using paired-pulse TMS protocols. Two final studies explored the effects of ETU and ITU on two classic areas in human information-processing: first, the ability to estimate and respond to ETU and ITU on a reward-based decision making task, and second whether multiple cues, informative about the correct time for action, increase precision in action timing through cue integration (thus reducing ITU). Results reveal that ETU and ITU are two qualitatively different types of constraint on action. They differ in their effects on action preparation and their interactions with event uncertainty. In choice situations, participants estimate ITU accurately but are biased regarding ETU. When there are multiple cues informative about action timing, participants use the most informative cue only. There are thus important differences between how people respond to temporal uncertainty arising from the external world and temporal uncertainty intrinsic to the *generative* processes within the action.

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Because it is the people you travel with you who make all the difference. They allow walking the road less traveled by, the road of a PhD, to its very end. And it is *that* road which leads to the more exciting places than the trodden paths. Thanks.

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Chapter 1: Time & Temporal Uncertainty in Cognition & Motor Control

Abstract: Time is a fundamental dimension of cognition and motor control. Limited information about the timing of future imperative events, or the appropriate time for motor action, induces *temporal uncertainty* and affects performance and expected action outcome. There are two types of temporal uncertainty distinguished by origin. If temporal uncertainty is due to a unpredictable world then there is *external temporal uncertainty* (ETU). *Internal temporal uncertainty* (ITU) arises due to humans' limited ability to estimate time at high accuracy. We first introduce ETU and ITU, highlight their differences, and putative differential effects on cognition and behaviour. Second, we discuss the general role of timing in cognition and motor control, in particular (i) different temporal scales, (ii) neural substrates and (iii) implicit versus explicit perceptual and motor timing. In subsequent sections, which introduce the questions pursued in the individual chapters of this thesis. We address first the effects of ETU and ITU on temporal expectation and action preparation and then the possible interaction between ETU, ITU, and uncertainty about the *type* of forthcoming motor action (*event uncertainty*). Third, we discuss effects of ETU and ITU on changes in corticospinal excitability (CSE) measured by transcranial magnetic stimulation (TMS), which is a neural measure of motor preparation. We also give brief general introduction to TMS and single- and paired-pulse techniques to measure CSE and intra-cortical inhibition. We conclude the chapter with a brief introduction to the role of ETU and ITU in decision-making and how one may reduce ITU and improve timing by combining information from multiple temporal cues.

Keywords: temporal uncertainty, external temporal uncertainty, internal temporal uncertainty, event uncertainty, action preparation, foreperiod paradigm, choice reaction time, decision-making under uncertainty, cue combination

Cassandra and Nostradamus are known, revered, perhaps even feared for their alleged ability to see into future. Predicting the future, however, is not as rare an ability as one might initially think. In fact, we all do it (Nobre, Correa, & Coull, 2007). The ability to prepare for future events, or to make decisions guided by their expected outcome, relies on our ability to predict such events, their timing, and their outcome. Advance information about the *timing* of future events induces *temporal expectation* and allows for *temporal preparation* (Coull, Cheng, & Meck, 2011; Nobre, Correa, et al., 2007). If such information is limited or absent, then one experiences *temporal uncertainty* (Klemmer, 1956, 1957). Temporal uncertainty affects temporal expectation, preparation (Niemi & Naatanen, 1981), and decision-making (Hudson, Maloney, & Landy, 2008).

This thesis is concerned with how we extract and use advance information about future events or forthcoming action to predict their timing under conditions of temporal uncertainty. In other words, we here explore how temporal uncertainty affects temporal expectation, temporal preparation, the timing of actions, and decision-making. We here limit ourselves to the investigation of time interval durations ranging from several hundred milliseconds up to a few seconds (500ms – 5s), typically known as *interval timing* (Buhusi & Meck, 2005; Mauk & Buonomano, 2004).

Importantly, there are two different types of temporal uncertainty (Klemmer, 1956, 1957): *external temporal uncertainty* (ETU) and *internal temporal uncertainty* (ITU). ETU arises when the timing of events varies from one instance to the next. Under such conditions, their timing can be predicted with limited accuracy only. We refer to this type of temporal uncertainty as *external* because it is due to variability arising from the external world. ITU, by contrast, has an *internal* origin. ITU arises as a consequence of limited accuracy in time perception, or put differently, a noisy internal clock(s).[1] Accuracy in time perception decreases in proportion to the increase in time interval duration, also known as the *scalar property of time*, a strong form of Weber's law applied to interval timing (Gibbon, 1977; Gibbon & Allan, 1984; Lejeune & Wearden, 2006, 2006; Lewis & Miall, 2009). Typically, this decrease in accuracy (i.e. this increase in variability) is directly proportional to time interval duration, although one study has reported disproportionally high inaccuracy for short (< 500 ms) time interval durations (Lewis & Miall, 2009a).

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[1] By referring to and 'internal clock', we do not want to express a commitment to either the pulse accumulator model (Allman & Meck, 2011), the striatal beat frequency model (Buhusi & Meck, 2005), or any other dedicated single (neural) mechanism that measure time (as opposed to intrinsic and / or distributed; Ivry & Schlerf, 2008). 'Internal clock' here refers to the ability to keep track of, measure, and perceive time, which is limited in accuracy.

ETU and ITU often occur in conjunction. Whenever participants prepare and respond to imperative events that vary in time (ETU), then they are often also required to measure and estimate time interval duration, which is intrinsically associated with ITU. Consequently, previous studies have predominantly looked at combined effects of ETU and ITU on temporal expectation and preparation (Bertelson, 1967; Bertelson & Tisseyre, 1968; Los, Knol, & Boers, 2001; Vallesi & Shallice, 2007) and their neural correlates (Correa & Nobre, 2008; Coull, Frith, Büchel, & Nobre, 2000; Cui, Stetson, Montague, & Eagleman, 2009; Miniussi, Wilding, Coull, & Nobre, 1999; Praamstra, Kourtis, Kwok, & Oostenveld, 2006; Tandonnet, Burle, Vidal, & Hasbroucq, 2003; Vallesi, McIntosh, Shallice, & Stuss, 2009; Vallesi, Shallice, & Walsh, 2007) with two notable exceptions (Klemmer, 1956, 1957). We here distinguish between ETU and ITU to explore their differential contribution to behaviour, in particular temporal expectation, temporal preparation, timed action, and decision-making.

Introduction to external and internal temporal uncertainty

Both ETU and ITU limit the extent to which one can predict the timing of future imperative events, or the appropriate time for action in case such events are missing as action-triggers. ETU and ITU are equivalent in their contribution towards the overall temporal uncertainty and, if action outcome depends on temporal uncertainty, expected reward. As such, they are both likely to influence temporal expectation, temporal preparation, and timed action: high temporal uncertainty, regardless of origin, is likely to interfere with temporal preparation (see Chapter 2 to 5) and / or accurately timed motor action (see Chapter 6 and 7). But ETU and ITU are fundamentally different in their origin. As a consequence, they also differ with regard to the following three aspects: first and foremost, ETU and ITU differ in type and number of informative cues that can be used to reduce either ETU or ITU. ETU can be reduced through learning statistical regularities inherent in one’s environment. There may be non-imperative events (i.e. events that do not require a motor response) that are informative about the timing of future imperative events (i.e. *endogenous cues*; Coull et al., 2000; Rohenkohl, Coull, & Nobre, 2011). For example, ‘ready’ and ‘set’ inform a sprinter about the impending imperative ‘go’-signal. Learning the informational ‘value’ of endogenous cues reduces ETU and is likely to improve temporal preparation and / or accurately timed motor action. In addition, imperative events themselves may be predictive about the timing of subsequent imperative events (i.e. *exogenous cues*; Coull et al., 2000; Rohenkohl et al., 2011), for example, when the time interval in between two subsequent imperative events is constant (Bertelson & Tisseyre, 1968) or follows an otherwise predictable pattern (Praamstra et al., 2006; Sakai et al., 2000). Finally, the mere passage of time may serve as a cue for temporal preparation (Nobre, Correa, et al., 2007). Typically, the probability of imperative events changes over time. For example, the probability of a red traffic light turning green rises over time. Changes in the probability of imperative events over time are commonly referred to as the hazard function (Coull et al., 2011; Nobre, Correa, et al., 2007). Learning the hazard function may contribute to a reduction of ETU and is likely to improve temporal preparation and accurately timed actions (Bueti, Bahrami, Walsh, & Rees, 2010; Janssen & Shadlen, 2005). Taken together, endogenous and exogenous cues as well as the hazard function reduce ETU and are likely to have beneficial effects on temporal preparation and accurately timed motor action in the face of temporal uncertainty.

ITU by contrast arises due to limited accuracy in time interval perception: it has an internal origin. ITU can be reduced by supplementing noisy internal clocks with more accurate external clocks (Borst & Cohen, 1987, 1989; Carlsen & Mackinnon, 2010). If a bus is scheduled to arrive in ten minutes time, then having a watch will allow for a more precise prediction about its time of arrival. Alternatively, multiple events presented sequentially may reduce ITU by sub-dividing otherwise long time intervals, thereby effectively shortening time interval duration (Requin & Granjon, 1969). Finally, multiple cues, all informative about the time to respond, may reduce ITU if their information is combined (Elliott, Wing, & Welchman, 2010; Ernst & Banks, 2002; Ernst & Bülthoff, 2004; Wing, Doumas, & Welchman, 2010); a possibility which we explore in the final chapter of this thesis (Chapter 7). Otherwise, if no measures are taken to remove ITU, then there will be ITU potentially impacting on performance, in particular whenever performance critically depends on the estimation of time interval duration, either implicitly or explicitly (Coull & Nobre, 2008; Nobre, Correa, et al., 2007). Whereas ETU has to be *induced* by the experimental design (i.e. by adding variability), the experimental design has to be intentionally modified to *remove* ITU. Consequently, many studies have looked at effects of ETU and ITU in conjunction only (Bertelson & Tisseyre, 1968; Coull et al., 2000; Los & van den Heuvel, 2001; Los & Agter, 2005; Los & Heslenfeld, 2005; Los & Schut, 2008; Los et al., 2001; Miniussi et al., 1999; Steinborn, Rolke, Bratzke, & Ulrich, 2008; Vallesi & Shallice, 2007; Vallesi, Mussoni, et al., 2007; Vallesi, Shallice, et al., 2007) with a few notable exceptions (Borst & Cohen, 1987, 1989; Carlsen & Mackinnon, 2010).

Second, ETU and ITU may differ in familiarity. ITU depends on the precision of one's time keeping abilities. Plenty of experience, throughout the course of one's lifetime, in having to measure and estimate time interval duration may have allowed participants to form accurate estimates of ITU. Consequently, participants may have developed strategies to cope with ITU to form temporal expectations and to prepare in time for imperative events despite ITU. In contrast, ETU is a property of the environment and has to be learned anew for each novel environment. Differences in familiarity may lead to different behavioural strategies in coping with ETU and ITU. For example, high familiarity may lead to overconfidence, which may cause an underestimation of ITU (Mamassian, 2008). Also, ETU and ITU may differentially interfere with non-temporal aspects of performance, perhaps due to differences in familiarity. For example, high ETU may interfere with using advance information about, for example, the *type* of forthcoming motor response (event uncertainty) while participants may have learned to cope with high ITU, due to prolonged experience, to avoid such interference.

Third, as a property of the environment, ETU may change over time. Changes in ITU are less likely, occur over larger time scales (e.g. ageing, see McAuley, Miller, Wang, & Pang, 2010; Turgeon, Wing, & Taylor, 2011) or only in pathological status (Allman & Meck, 2011; Coull et al., 2011). Consequently, participants may choose different strategies to cope with ETU compared to ITU. Participants may rely on relatively recent information about ETU, for example, the timing of the last preceding imperative event, to detect and respond to changes in the temporal structure of one's environment flexibly. Such strategies to cope with ITU are unlikely.

And finally, ETU and ITU may interact in their effects on behaviour. For example, learning about temporal regularities in one's environment requires a sense of time sufficiently accurate to pick up on the temporal structure of events. In other words, high ITU may interfere with attempts to reduce ETU. Also, an underestimation of ITU, due to high familiarity, may in turn lead to exaggerated estimates of ETU (perhaps to preserve a correct estimate of overall temporal uncertainty: ETU + ITU). While the effects of ETU and ITU have previously been studied in conjunction, here we explore differential effects of ETU and ITU on behaviour: first, to highlight the importance of this theoretical distinction, second, to encourage further research into their differential effects on various areas in human information processing, and third to call attention to the fact that ITU may affect temporal and non-temporal aspects of behaviour on many tasks and paradigms if not explicitly controlled for.

Introduction to the multi-faceted nature of time

Carefully distinguishing between types of temporal uncertainty is important because time is a fundamental dimension of behaviour. Perceptions, actions, and our understanding of the world unfold over time (Wittmann, 2011). “Timing” is used to refer to not only when an event is going to happen (*temporal prediction*) but also, how long it is going to take (*duration estimation*), or whether it occurred before or after some other temporal reference (*order judgement*; Coull et al., 2011), thus highlighting the many different areas in which timing is important. Duration estimation and temporal prediction require a *metrical* representation of time whereas an *ordinal* scale suffices to establish temporal order (Coull et al., 2011). We are here primarily concerned with behaviour that requires a metrical representation. Such representations of time are important for a wide range of behaviour that develop over different time scales: from hours, to minutes, seconds, and milliseconds.

Timing across difference temporal scales

Based on relevant time scales, and presumed underlying neural mechanisms, temporal processing can be categorised into four different time scales: circadian rhythms, interval timing (i.e. second processing), sub-second (i.e. millisecond), and microsecond processing (Buhusi & Meck, 2005; Mauk & Buonomano, 2004). *Circadian rhythms* operate over 24 hour cycles and control sleep and wakefulness as well as metabolic and reproductive fitness. In mammals, the clock that drives circadian rhythms is located in the suprachiasmatic nucleus of the hypothalamus (Morse & Sassone-Corsi, 2002). This clock modulates behaviour according to, for example, light input (Rongmin Chen, Seo, Bell, von Gall, & Lee, 2008; Reppert & Weaver, 2002) or social information (Levine, Funes, Dowse, & Hall, 2002).

Interval timing, by contrast, operates over a much smaller time scale, ranging from a couple of hundreds of milliseconds (> 500ms – 1s; Gutyrchik et al., 2010; Mauk & Buonomano, 2004) to a few seconds or minutes (Buhusi & Meck, 2005). Interval timing is important for a wide range of behaviour, from foraging (Kacelnik & Brunner, 2002) and decision making (Balci, Freestone, & Gallistel, 2009; Hudson et al., 2008), to arithmetic performance (Sohn & Carlson, 2003), and several aspects of motor control (Bertelson, 1967; Bertelson & Tisseyre, 1968; Carlsen & Mackinnon, 2010; Cui et al., 2009; Drazin, 1961; Los et al., 2001; Vallesi & Shallice, 2007). The neural correlate of interval timing it a matter of debate, despite numerous neuroimaging (Correa & Nobre, 2008; Coull et al., 2000; Coull & Nobre, 2008; Harrington, Castillo, Fong, & Reed, 2011), neuropsychological (Artieda, Pastor, Lacruz, & Obeso, 1992; Pastor, Artieda, Jahanshahi, & Obeso, 1992; Vallesi, Mussoni, et al., 2007), and neuropharmacolgical studies (Rammsayer, 1993; Rammsayer & Vogel, 1992). Most likely, interval timing depends on the basal ganglia, in particular the striatum, and intact dopaminergic neurotransmission (Jahanshahi, Jones, Dirnberger, & Frith, 2006; Jahanshahi et al., 2010; Jones & Jahanshahi, 2009; Jones, Malone, Dirnberger, Edwards, & Jahanshahi, 2008). Further, the supplementary motor cortex (SMA; Mita, Mushiake, Shima, Matsuzaka, & Tanji, 2009; Wencil, Coslett, Aguirre, & Chatterjee, 2010) in conjunction with the pre-SMA (Macar, Coull, & Vidal, 2006) have been implied in interval timing, in addition to the right prefrontal cortex, in particular the right dorsolateral prefrontal cortex (rDLPFC; Jones, Rosenkranz, Rothwell, & Jahanshahi, 2004; Vallesi & Shallice, 2007; Vallesi, Mussoni, et al., 2007; Vallesi, Shallice, et al., 2007).

Sub-second (< 1s), or *millisecond timing* (< 500ms) is crucial for motor control (Schlerf, Spencer, Zelaznik, & Ivry, 2007), speech generation and recognition (Schirmer, 2004), playing music and dancing (Thaut et al., 2009). The cerebellum may underlie sub-second timing (Buhusi & Meck, 2005), in particular when tasks require discretely timed motor responses (Schlerf et al., 2007), or estimation of absolute (i.e. how long?), as opposed to relative, time interval estimation (i.e. longer or shorter?; Grube, Lee, Griffiths, Barker, & Woodruff, 2010; Teki, Grube, Kumar, & Griffiths, 2011). *Microsecond timing* underlies sound localisation and echolocation and depends on axonal conduction delays (Heinrich, Warmbold, Hoffmann, Firzlaff, & Wiegrebe, 2011).

While there is thus abundant evidence that circadian rhythms and microsecond timing are supported by distinct neural mechanisms, the distinction between interval timing and millisecond timing is less clear-cut. It is supported by, for example, neuropsychological studies: Parkinson disease (PD) patients show impaired interval timing, compared to healthy controls, on a variety of tasks (Artieda et al., 1992; Jurkowski, Stepp, & Hackley, 2005; Koch et al., 2008; Pastor et al., 1992; Smith, Harper, Gittings, & Abernethy, 2007). By contrast, in the millisecond range, performance of PD patients is comparable to that of healthy controls (Wearden et al., 2008). Further, neuropharmacological studies have revealed that remoxipride, a dopamine antagonist more selective for D2 receptors, impairs temporal processing on temporal scales of one second and above while temporal processing below one seconds is largely unaffected (Rammsayer, 1997). Similarly, benzodiazepines affect temporal processing on timescales of one second and beyond whereas millisecond timing is largely preserved under pharmacological challenge (Rammsayer, 1999; Rammsayer & Vogel, 1992). Finally, a recent study has found that left hand dominance is associated with underestimation of supra- but not sub-second intervals (Vicario, Bonní, & Koch, 2011).

In line with these findings, Wing and Kristofferson have reported a discontinuity in timing behaviour suggestive of two timing mechanisms for different temporal scales: accuracy in time perception does not change for time intervals below 250ms, a violation of Weber's law applied to interval timing (Wing &

Kristofferson, 1973). Others, however, have tried and failed to find such discontinuities in timing behaviour (Lewis & Miall, 2009a). Further, the cerebellum, typically associated with millisecond timing, is co-activated also during interval timing (Coull & Nobre, 2008). Similarly, the basal ganglia, typically associated with interval timing, have been implied in millisecond timing (Shih, Kuo, Yeh, Tzeng, & Hsieh, 2009). The distinction between interval and millisecond timing remains a matter of debate.

Some have suggested that differences in behaviour, in clinical populations or under neuropharmacological challenge, arise due to a higher recruitment of working memory and / or attention for longer versus shorter time intervals (Coull et al., 2011). If, for example, a certain drug interacts with working memory, and if working memory is more strongly recruited for supra-second timing, then behaviour will be impaired for supra- but not sub-second timing. Interestingly, Lewis and Miall prevented participants from using cognitive strategies for longer versus shorter time intervals (e.g. spontaneous 'counting') thus reducing possible effects of working memory or attention. In contrast to Wing and Kristofferson, they did not find a discontinuity in behaviour suggestive of a distinction between sub- and supra-second timing (Lewis & Miall, 2009a). Further studies are need that tightly control for differences in working memory and attention for long versus short timescales to elucidate the neural substrate of sub- versus supra-second timing.

We here limit ourselves to the study of interval timing, in particular the influence of ETU and ITU on interval timing as important for accurately timed motor preparation or reward-based choice. The time intervals, employed in the research presented here, range from 500ms up to 5s. We acknowledge that shorter time intervals may be entirely, or partially, supported by different mechanisms or neural substrates than longer time intervals. But crucially, the scalar property of time interval duration, the origin of ITU, holds for short (500 – 1000ms), intermediate (1000 –

3000ms) and long (3000ms – 6000ms) time intervals (Lewis & Miall, 2009a). In studying the effects of ETU and ITU on behaviour (or a neural measure of motor excitability using TMS), we remain impartial to the debate whether or not different neural substrates support sub- versus supra-second timing.

Perception of time & clocks in the brain

While we are able to perceive time, we lack a dedicated sense it. So how do we measure time? The predominant model for interval timing has been the *pulse-accumulator model* (also *Scalar Expectancy Theory* or *Scalar Timing Theory*). This model divides temporal processing into clock, memory, and decision processes. The clock component, an accumulator, measures time by collecting pulses or 'clock ticks', emitted from an oscillator. The number of accumulated pulses thus represents time. A 'switch' closes at the onset of a to-be-timed signal, which allows pulses to accumulate in the accumulator. Once the signal ends, or acquires some other significance (e.g. positive feedback), the accumulated pulses are transferred from the accumulator to reference memory for future use. If the duration is presented or experienced again, then the current contents of the accumulator are compared against the pulse-trains stored in reference memory. The reference memory contains a distribution of pulse-trains for each given interval duration. A ration-decision rule operates to determine whether the current pulse-train is sufficiently similar to a randomly chosen reference pulse-train of a given duration. This distribution of pulse trains in reference memory, in combination with the ratio decision rule, gives rise to the scalar variability in interval timing and thus ITU.

The *striatal beat frequency theory* is essentially a neural instantiation of the pulse-accumulator model (Allman & Meck, 2011). According to the striatal beat frequency theory, time interval estimation is based upon coincidence detection (the decision component), carried out by medium spiny neurons in the striatum (i.e. the main input station / cells of the basal ganglia), of patterns of oscillatory neurons in the cortex. Populations of cortical neurons phase re-set (i.e. synchronise) at the onset of a to-be-timed signal and start oscillating at their endogenous frequency (the clock component). At the same time, the level and activity of medium spiny neurons is reset by phasic dopaminergic input from the ventral tegmental area and substantia nigra pars compacta. If the to-be-timed signal ends, or acquires some other significance, a pulse of dopamine strengthens the cortico-striatal synaptic weights that are activated by the specific oscillatory pattern of cortical neurons at that specific moment in time (the memory component). Thereby, medium spiny neurons become tuned to specific patterns of oscillatory activity, which come to represent time interval duration. Later, medium spiny neurons compare current oscillatory patterns to the ones that were reinforced previously. If there is a match between current and previously reinforced oscillatory patterns, medium spiny neurons signal coincidence of oscillatory patterns, or, in other words, sufficient similarity of to-be-timed intervals, and indicate hereby, e.g. the appropriate time for a response (Buhusi & Meck, 2005).

The pulse-accumulator model, and its neural instantiation, the striatal beat frequency theory, are instances of *dedicated models* of time perception, as opposed to *intrinsic models*. Dedicated models entail specialised mechanisms that measure or represent temporal information. Some dedicated models of time perception also entail neural structures that are specialised to represent temporal information, for example the cerebellum (Ivry, Spencer, Zelaznik, & Diedrichsen, 2002) and / or the basal ganglia (Buhusi & Meck, 2005). However, a dedicated time system may also involve activity in a widely distributed network of neural regions (Ivry & Schlerf, 2008). Within these models, some areas may be involved in representing temporal information only (e.g. pulse accumulation), whereas others might sub-serve more general functions (e.g. memory components).

Intrinsic models, by contrast, do not assume that there are specialised mechanisms or brain structures that measure or represent temporal information. Intrinsic models entail that time is inherent in neural dynamics. For example, neuronal populations that can sustain activity in the absence of sensory information may encode temporal information, for example in the motor and pre-motor cortex (Lebedev, O'Doherty, & Nicolelis, 2008; Renoult, Roux, & Riehle, 2006). Similarly, memory strength may underlie temporal processing: time interval duration may be inferred from the decay in memory strength over time (Staddon, 2005).

The debate about dedicated versus intrinsic models of time perception is not yet resolved. The ability to compare time interval duration across modalities supports models that entail an amodal representation of time (S Grondin & Rousseau, 1991; Ulrich, Nitschke, & Rammsayer, 2006). Also, individual difference in accuracy of time perception and reproduction correlate between perception and action (Keele, Pokorny, Corcos, & Ivry, 1985) suggesting an amodal timing mechanism. In contrast, neuroimaging studies that show differential activation for time interval perception in the visual, auditory, or motor domain support modality specific models (for a comprehensive meta-analysis, see (Wiener, Turkeltaub, & Coslett, 2010). Interestingly, a recent study revealed impaired performance on a visual time estimation task when the auditory cortex was stimulated using repetitive TMS. This suggests a supra-modal role of the auditory cortex during time interval perception (Kanai, Lloyd, Bueti, & Walsh, 2011).

Here, we do not commit to a specific model of time perception. We study the effects of ETU and ITU on cognition and motor control. We address the issue of modality specific versus supra-modal clocks only in the final chapter of this thesis (Chapter 7), when we explore whether one can reduce ITU by integrating temporal information from multiple cues. When assessing the neurophysiology of preparation under conditions of ETU, we measure neural activity in the primary motor cortex as an index of motor preparation (Chapter 4 & 5). This does not imply, however, that we assume that time perception takes place in the primary motor cortex exclusively. Other brain areas, close or distal, may drive the changes in activity in the primary motor cortex. Importantly, the term “internal clock” is used here to refer to the capacity to perceive and measure time (see footnote 1). By using the term “internal clock”, we do not express a commitment to a dedicated model of time perception, such as the pace-accumulator model.

Explicit timing versus implicit temporal expectations

Some tasks require *explicit* estimates of time interval duration whereas others rely on *implicit* time interval estimates to achieve high levels of performance (for an overview, see Figure 1.1). *Explicit interval timing* is recruited whenever the accurate estimation of time is the main goal of the current task: explicit timing thus requires overt estimates of stimulus or time interval duration. In experimental settings, participants may be required to perceptually discriminate time intervals of various durations, for example, when performing an explicit *perceptual* timing task (e.g. time interval reproduction). Alternatively, participants may be asked to reproduce time intervals on explicit *motor* timing task (Jazayeri & Shadlen, 2010; Lewis & Miall, 2009a). In these tasks, the stimuli that participants respond to can occur in any modality: visual, auditory, or tactile. Time perception is typically more accurate in the auditory compared to the visual or tactile modality (Elliott et al., 2010; Wing et al., 2010). For that reason, sound dominates timing of audio-visual stimuli on explicit timing tasks (Burr, Banks, & Morrone, 2009).

By contrast, *implicit interval timing* is recruited when accurate estimates of time interval duration contribute to improved performance related to some non-temporal goal. For example, a sprinter benefits from being able to predict the timing of the ‘go’-signal, because this prediction allows her to optimise and align motor preparation with the imperative event. There are implicit *perceptual* and *motor* timing tasks. On implicit perceptual timing tasks, participants are typically required to respond to visual, tactile, or auditory stimuli, for example on foreperiod tasks (for a review, see (Niemi & Naatanen, 1981). Participants are able to prepare more efficiently and respond more quickly if they can predict the timing of the imperative sensory event. On motor timing tasks, estimates about time interval duration may contribute to the regularity of motor output (e.g. on continuous circle drawing tasks). The scalar property of interval timing, first reported for explicit timing tasks (Lewis & Miall, 2009a), is engaged also in implicit timing (Piras & Coull, 2011). Time perception decreases in accuracy with increasing time interval duration. ITU increases with increasing time interval duration for both explicit and implicit timing.

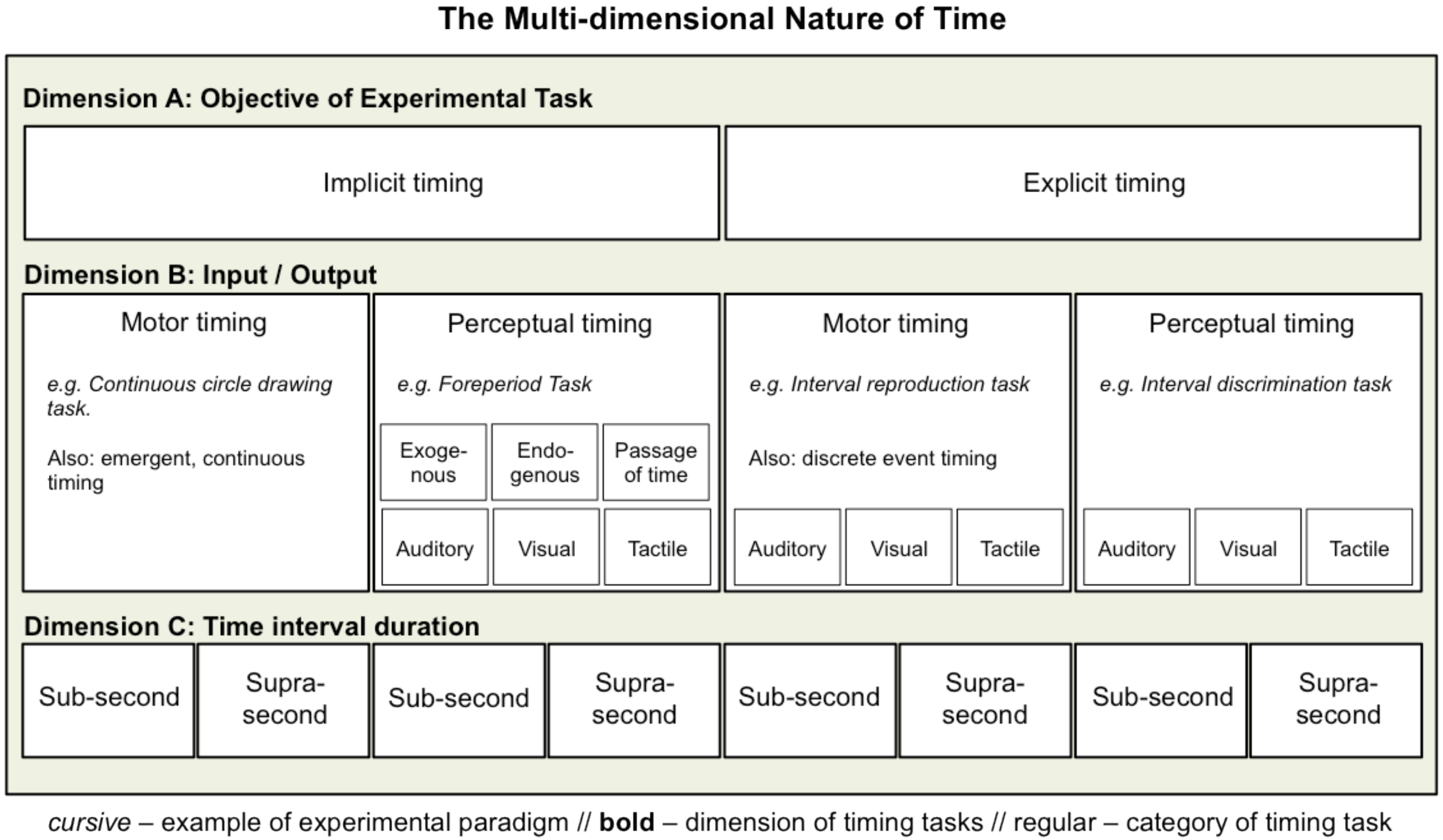


Figure 1.1: Time is a fundamental dimension of behaviour. Tasks that require overt estimates of time interval duration recruit explicit timing. If accurate time perception contributes to non-temporal performance, then participants engage in implicit timing. Stimuli that demarcate time intervals on explicit timing tasks, or that prompt participants to respond on implicit timing tasks, can be delivered in the auditory, visual or tactile modality. On implicit perceptual timing tasks, participants can use three different types of cues to reduce external temporal uncertainty (ETU). Exogenous cues are stimuli that, while prompting a motor response, are informative about the timing of future responses. Endogenous cues do not prompt a response but provide information about the timing of future imperative stimuli. The passage of time can serve as a cue because the probability of imperative events usually changes across time: when waiting at a traffic light, the switch to green gets increasingly more likely the longer one waits. Finally, tasks can be distinguished by the time interval duration that they predominantly employ. Some postulate different mechanism and neural correlates for sub- versus supra-second timing.

The neural correlate of timing may depend on whether participants perform an explicit versus implicit timing task (Coull & Nobre, 2008). Explicit interval timing specifically activates the basal ganglia, with co-activation of prefrontal, premotor, and cerebellar areas. By contrast, implicit timing recruits cortical action circuits, such as inferior parietal and premotor areas (Coull & Nobre, 2008). Thus, the neural correlate of timing may not only depend on the timescale (sub- versus supra-second), modality (auditory, visual, etc.) but also on the goal of the task that participants engage in. In the work presented here, we use a variety of explicit and implicit timing tasks. Explicit timing tasks allow estimation of participant's variability in time perception and consequently the level of ITU they experience associated with particular time interval durations. We use implicit timing tasks, by contrast, to study effects of ETU and ITU on temporal expectation and preparation.

Preparation for action under conditions of ETU and ITU

Temporal uncertainty lowers the predictability of the timing of imperative events and detrimentally affects motor preparation and execution. Effects of temporal uncertainty on temporal preparation have been studied with the foreperiod paradigm (for a review, see Hackley, 2009; Niemi & Naatanen, 1981). In this paradigm, a warning signal (WS) is followed by an imperative signal (IS), which prompts a motor action. The time interval between the WS and the IS is called the foreperiod (FP). Below, we summarise the main features and behavioural signatures of two frequently used variants of the FP paradigm, the *constant* and the *variable* FP paradigm.

Constant and variable foreperiod paradigms to study action preparation

In constant FP paradigms, one fixed FP is used across all the trials of a single block (Niemi & Naatanen, 1981). In this case, ETU is eliminated because the timing of the IS in relation to the WS does not vary. The duration of the FP determines the level of ITU: the longer the FP, the higher the level of ITU. Studies using constant FP paradigms show that reaction times increase with increasing FP duration (Bertelson & Boons, 1960; Klemmer, 1956, 1957). This suggests that participants cannot remain optimally prepared for long periods of time (Gottsdanker, 1975) and that preparation is a limited resource that should be 'spent' wisely (Steinborn et al., 2008). Due to noisy internal clocks, predicting the timing of the IS becomes more difficult when ITU is high (Klemmer, 1957). Consequently, it becomes more difficult to optimally align action preparation with the IS.

In variable FP paradigms, several FPs occur across the trials of a single block. This inter-trial variability in FP duration introduces ETU, in addition to ITU. Previous studies using variable FP paradigms have demonstrated three ways in which variable FP duration affects action preparation. First, they have shown an increase in reaction times with increasing FP variability (Drazin, 1961; Klemmer, 1957). Higher variability makes it more difficult to learn and predict the timing of the IS (Klemmer, 1956, 1957), which will impair the alignment of action preparation with the timing of the IS. Second, previous work has revealed that reaction times decrease with increasing FP duration (Bueti, Bahrami, Walsh, & Rees, 2010; Drazin, 1961; Los & van den Heuvel, 2001; Requin, 1969; Vallesi & Shallice, 2007), a feature commonly referred to as the *foreperiod (FP) effect*. Third, reaction times are influenced by the FP of the immediately preceding trial (Alegria & Delhaye-Rembaux, 1975; Los & Agter, 2005; Steinborn et al., 2008; Vallesi & Shallice, 2007; Van der Lubbe, Los, Jaśkowski, & Verleger, 2004), a feature referred to as *sequential effect(s)* (Drazin, 1961; Los & van den Heuvel, 2001; Los & Agter, 2005; Los & Heslenfeld, 2005; Los & Schut, 2008; Los et al., 2001; Steinborn et al., 2008).

Strategic and conditioning accounts of temporal preparation

The FP effect and sequential effects have been explained by three alternative and competing accounts (for an overview, see Figure 1.2): there are two *strategic accounts*, which explain these effects as consequences of deliberate adjustments in action preparation (Bertelson, 1967; Drazin, 1961; Vallesi et al., 2009), and one *conditioning account* (Los et al., 2001).

One of these strategic accounts suggests that the decrease in reaction times with increasing foreperiod duration (i.e. the FP effect) is due to an increase in the probability of IS occurrence over the course of a trial if the IS has not yet occurred (hazard function). In other words, participants may use the passage of time, and associated changes in conditional IS probability, for temporal preparation. Stronger FP effects with steeper FP distributions (in which the likelihood of the IS increases more quickly) support this suggestion (Los & Agter, 2005). Similarly, there is no decrease in reaction times with increasing FP duration when non-ageing FP distributions are employed (in which the conditional likelihood of the IS does not change; Trillenberg, Verleger, Wascher, Wauschkuhn, & Wessel, 2000). These findings suggests that participants adjust preparation according to changes in conditional IS probability. In case of optimal preparation, the decrease in reaction time should thus be directly proportional to the increase in conditional IS probability (i.e. the hazard function).

The second strategic account seeks to explain sequential effects and, as a by-product, the FP effect. It suggests that participants' default expectation is a FP repetition. Consequently, they are optimally prepared if such a repetition actually occurs. However, if the FP is shorter and the IS occurs unexpectedly early, participants are sub-optimally prepared and reactions will be slow. By contrast, if the IS occurs later than expected, then re-preparation is possible and no reaction time decrements are incurred from incorrectly assuming a FP repetition (Alegria, 1974;

Drazin, 1961; Vallesi & Shallice, 2007). As a by-product, responses will be faster for longer FPs than for shorter FPs because the latter are more negatively affected by the expectation of FP repetition than the former.

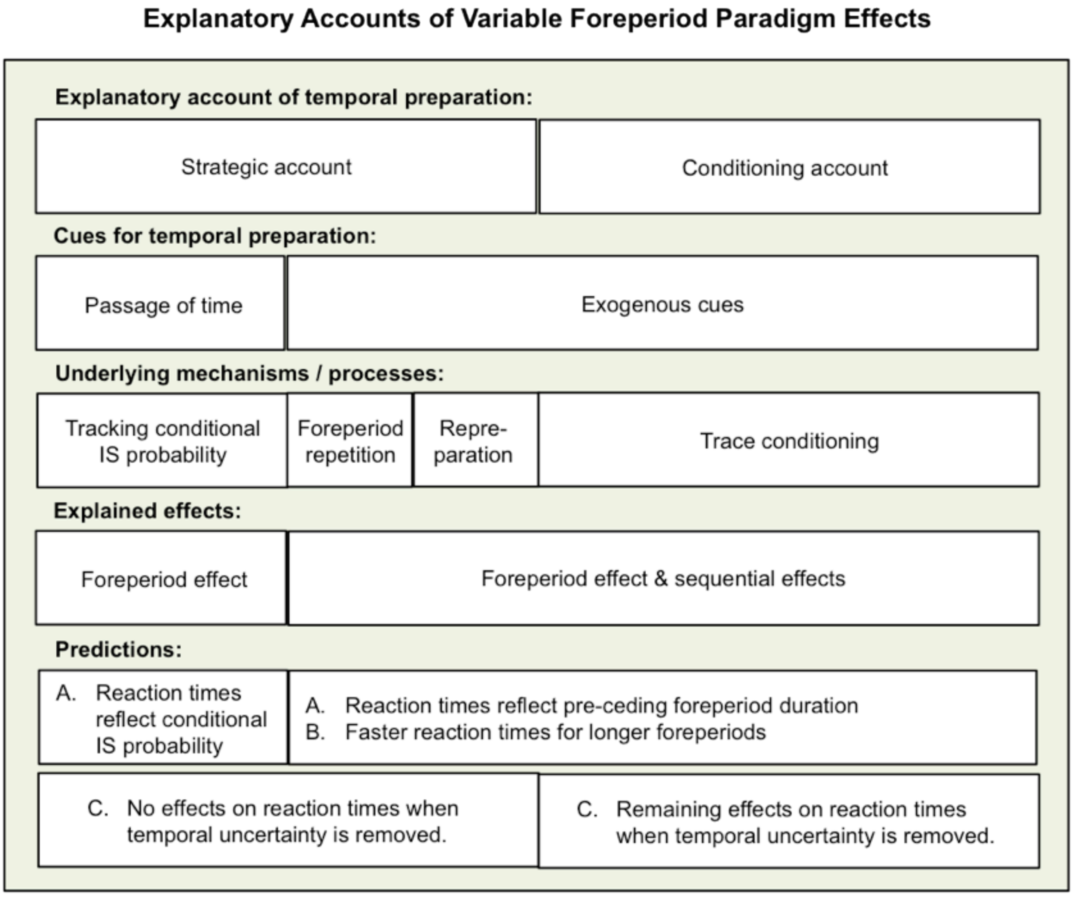


Figure 1.2: Three alternative and competing accounts explain behavioural effects on variable foreperiod (FP) reaction time tasks. Reaction times are affected in two ways: first, reaction times decrease with increasing FP duration (FP effect). Second, the duration of the foreperiod of an immediately preceding trial affects the reaction times on the subsequent trial as a function of the duration of the subsequent trial's FP (i.e. sequential effects). For example, if the subsequent trial's FP is shorter compared to the FP of the preceding trial, then reaction times increase. Two accounts explain these effects as strategic adjustments in preparation while the remaining third one explains the reaction time effects in terms of trace conditioning. The first strategic account states that the decrease in reaction times is due to an increase in the probability of the imperative stimulus with increasing FP duration (i.e. the conditional probability of the imperative stimulus). In the ideal case, reaction times should decrease in direct proportion to the increase in conditional probability of the imperative stimulus (i.e. hazard function). Note that this account explains the FP effect only. The second strategic account postulates that participants expect a repetition of just experienced foreperiod duration. If the foreperiod is shorter, then participants, in expecting a longer foreperiod, are not yet prepared to respond: reactions are slower. By contrast, if the foreperiod is longer than expected, then participants re-prepare and responses do not suffer from the incorrect assumption of foreperiod repetition. This account, designed to explain sequential effects, also accounts for the FP effect. The trace conditioning account explains both sequential effects and the FP effect. Preparatory activity is shaped by reinforcement and extinction. If the imperative event occurs some time after the warning stimulus, then that moment in time is reinforced and preparatory activity is higher at and around that moment in time on the subsequent trial. This explains the sequential effects. All moments in time *before* the imperative event are subjected to extinction. By contrast, preparatory activity associated with moments in time *after* the imperative event remains unaffected. This asymmetry in reinforcement and extinction explains the FP effect. The strategic accounts predict that explicit cues informative about the timing of the imperative event remove effects of temporal uncertainty. According to the trace conditioning account, effects should persist.

By contrast, the conditioning account explains temporal preparation as consequences of trace conditioning rather than strategic adjustments in response to (changing) information about the timing of the imperative event (e.g. Los et al., 2001; Los & van den Heuvel, 2001; Los & Heslenfeld 2005). Put simply, the IS is thought to act as an unconditioned stimulus that elicits a motor response. The WS acts as a conditioning stimulus that prompts preparatory activity. The time course of this preparatory activity following the WS is shaped by reinforcement and extinction determined by when the IS has occurred in the past. Central to this idea is that the moment of IS occurrence is reinforced, and preparatory activity on the following trial is therefore higher at and around that time. At the same time, moments *before* the IS are subject to extinction (Los, 2004), whereas preparatory activity for moments *after* the IS is not affected. Preparatory activity for earlier moments therefore decreases, but remains unchanged for later ones. Thus, there is an asymmetry between reinforcement and extinction for short versus long FPs: long FPs are subject to reinforcement only, short FPs are subject to both reinforcement and extinction. Finally, the conditioned response is assumed to have the scalar property (Los et al., 2001).

The single-process conditioning account can explain both the FP and the sequential effects (Los et al., 2001): reinforced preparatory activity from previous trials carries over to the next trial giving rise to the sequential effects. The FP effect is explained by the asymmetry in reinforcement and extinction. Responses for long FP are faster because they are subjected to extinction to a lesser extent than short FPs.

In principle, all three accounts may hold at the same time: participants may keep track of the conditional probability of the IS whilst being influenced by the FP duration of the previous trial (Alegria & Delhaye-Rembaux, 1975; Los & Agter, 2005).

A part of preparatory adjustments over time may be deliberate and a part conditioned and automatic. Because the conditioning account explains FP and sequential effects as consequences of trace conditioning, explicit and reliable cues informative about FP duration should not eliminate these effects (Los & van den Heuvel, 2001; Los & Heslenfeld, 2005). Indeed, several studies have reported attenuated but not eliminated FP and sequential effects when information about the duration of the FP was provided (Los & van den Heuvel, 2001; Los & Heslenfeld, 2005) supporting the single-process conditioning account.

By contrast, using the logic of double dissociation, recent neuropsychological studies (Vallesi, Mussoni, et al., 2007), developmental studies (Vallesi & Shallice, 2007), and work applying transcranial magnetic stimulation in a cognitive lesion paradigm (Vallesi, Shallice, et al., 2007) provide evidence that that sequential effects and the FP effect have a different origin and are supported by different neural substrates. Moreover, Los and colleagues could recently show that sequential effects can be reversed through different cognitive strategies (Los & Horoufchin, 2011). Collectively, these results suggest that the FP effect cannot be a mere consequence of the processes underlying the sequential effects (Vallesi, Mussoni, et al., 2007; Vallesi & Shallice, 2007; Vallesi, Shallice, et al., 2007), and favour the proposal that preparatory adjustments are, at least in part, due to changes in IS probability.

Taken together, previous studies on temporal preparation, using the constant or variable FP paradigm, have revealed how temporal uncertainty shapes temporal preparation. While different accounts can explain changes in preparation over time, they differ regarding the cues that are used for temporal preparation and underlying mechanisms. Importantly, however, neither explicitly addressed the role of the different sources of temporal uncertainty (i.e. ETU and ITU), and how these may affect the foreperiod or sequential effects, respectively. We single out effects of ETU and ITU on temporal expectation and preparation (Chapter 1). Further, we remove

ITU selectively to study effects of ETU in isolation (Chapter 1). Designed primarily to explore effects of ETU and ITU on temporal expectation and preparation, we aim to put the strategic and the conditioning account to the test.

Interaction between ETU, ITU and event uncertainty

ETU and ITU may not only affect temporal expectation and preparation. These two types of temporal uncertainty may also interact with the use of advance information about the *type* of the forthcoming imperative event, and consequently, the preparation of the appropriate motor response (*event preparation*). In other words, ETU and ITU may interact with uncertainty about the type of the forthcoming motor response prompted by the imperative event (*event uncertainty*).

Action preparation typically benefits from low event uncertainty. Choice reaction times, for example, are lower when there are only a few possible alternative responses compared to when there are many (Fitts, 1954; Fitts & Peterson, 1964; Hick, 1952; Hyman, 1953; Schneider & Anderson, 2011). There is evidence that event and temporal uncertainty independently affect action preparation. First, advance information about when to act is beneficial even if the response required by the environment does not correspond to the action that was prepared. For example, Holender and Bertelson found that frequent (75%) and infrequent (25%) responses prompted by imperative events benefit to the same extent from low temporal uncertainty (Holender & Bertelson, 1975) but see (Bertelson & Barzeele, 1965). Further, even when participants do not know what action to prepare, when action alternatives are equally likely, preparation still benefits from information about when to act (Bertelson & Boons, 1960).

Second, information about when to act improves action preparation even if the imperative event is incompatible with the motor response prompted by it. For example, Spijkers and Walter manipulated semantic stimulus-response compatibility, foreperiod duration, and movement duration (Spijkers & Walter, 1985). Imperative stimuli, after a constant foreperiod, instructed short or fast sliding movements. Participants were instructed to respond to an imperative stimulus that instructed a fast movement with a fast (compatible) or slow sliding movement (incompatible) or vice versa. The effects of stimulus-response compatibility, foreperiod duration, and movement duration were strictly additive (see also Meulenbroek & Van Galen, 1988; Spijkers, 1990).

Third, two neuroimaging studies suggest that the beneficial effect of knowing when to act does not depend on knowing what action to prepare. For example, Sakai et al. instructed participants to respond to auditory or visual stimuli with index or middle finger responses (Sakai et al., 2000). In one condition, the order of stimuli alternated; impending actions were fully predictable and event uncertainty was thus fully removed. In another condition, the order of stimuli was random and event uncertainty thus high. In addition, stimuli occurred after constant (i.e. low temporal uncertainty) or variable (i.e. high temporal uncertainty) foreperiods. Similarly, Cotti et al. used a variable foreperiod 2-choice reaction time task and removed event or temporal uncertainty by explicitly cueing either the motor action, or the duration of the foreperiod (Cotti, Rohenkohl, Stokes, Nobre, & Coull, 2011). Both studies report additive effects of event and temporal uncertainty. In addition, these studies report separable neural correlates for preparation for what to do and preparation for when to do it (Cotti et al., 2011; Sakai et al., 2000).

These studies taken together thus suggest that preparation for *what* to do and preparation for *when* to do it are supported by two independent processes (Holender & Bertelson, 1975) which may take place at different and discrete processing stages (Sanders, 1990; Spijkers, 1990; Spijkers & Walter, 1985). Separable neural correlates for preparation for *what* to do and for *when* to do it are in agreement and further support this proposal. However, both Sakai et al. and Cotti et al. have also reported shared neural correlates for preparation under temporal and event uncertainty (Cotti et al., 2011; Sakai et al., 2000). This suggests that the processing of temporal and event uncertainty for action preparation may not be entirely independent. More fundamentally, one problem of previous work is that the distinction between ETU and ITU was neglected. At the behavioural level, putative interaction effects between event and temporal uncertainty may cancel out when both ETU and ITU are experienced in conjunction (Bertelson & Boons, 1960; Sakai et al., 2000). For example, participants may benefit more from low ETU when event uncertainty is low, because they are then able to prepare the appropriate action at the appropriate time. By contrast, participants may be able to compensate for high ITU when they are not also simultaneously hampered by high event uncertainty. In chapter 3, we present a study on the interaction between ETU, ITU, and event uncertainty and demonstrate that indeed, the relation between event and temporal uncertainty depends on the *origin* of temporal uncertainty.

The neurophysiology of action preparation under temporal uncertainty

Effects of temporal expectation and preparation may be due to either sensory or motor preparation (Rolke & Ulrich, 2010). In the first case, knowing the timing of imperative events would positively influence the *perception* of imperative stimuli. In the latter case, *motor preparation* would benefit from advance information about action timing. Of course, advance information may affect both, sensory and motor processes. While there is some evidence that advance information about the forthcoming event and its timing affects sensory processing (Rolke & Ulrich, 2011), there is ample evidence for a contribution of motor preparation to the effects of temporal expectation. Using *Transcranial Magnetic Stimulation* (TMS) to probe neural excitability of the primary motor cortex, we explore the contribution of the motor system to temporal preparation.

Introduction to Transcranial Magnetic Stimulation (TMS)

TMS is a powerful technique that allows probing, for example, neural excitability, plasticity, and functional connectivity of the brain non-invasively in healthy and clinical populations. TMS equipment consists of a TMS stimulator and a TMS coil. The fundamental operating principle of a TMS stimulator is to create a changing current in the TMS coil, which produces a changing magnetic field that, in turn, can induce a current in adjacent conductive tissue (e.g. cortical tissue), as prescribed by Faraday's law (Epstein, 2008). If the TMS coil is placed upon the scalp, then this induced current interacts with cortical and, to a lesser extent, sub-cortical neurons. At the heart of this interaction, there is a transfer of charge across the nerve membranes. Positive ions are driven into the cell, its intracellular potential rises, and if the rise is sufficient, an action potential results (Davey, 2008).

Traditionally, TMS has been used to measure or "read out" neural excitability, primarily by giving one single TMS pulse over the primary motor cortex (M1) whilst recording electromyographic activity (EMG) in the stimulated *target muscle*. In addition, TMS allows the non-invasive study of intra-cortical (i.e. paired-pulse TMS) as well as inter-hemispheric inhibitory and excitatory circuits (i.e. double-coil TMS). Further, using two TMS coils, one can study the functional connectivity of the brain by measuring the effect of a conditioning pulse, delivered to an area other than M1, on the MEP elicited by a single TMS pulse over M1. Repetitive TMS (e.g. 1Hz, 5Hz) induces changes in neural activity of the stimulated area and allows, as such, the non-invasive study of brain plasticity. Finally, in combination with behavioural experiments, TMS can be used to explore the functional relevance of a particular brain area to specific behaviour in *cognitive lesion paradigms* (Walsh & Cowey, 1998). We here limit ourselves to the discussion of on single and paired-pulse TMS protocols.

Using TMS to measure neural excitability

Single-pulse TMS over the primary motor cortex elicits a *motor-evoked potential* (MEP) in the target muscle. The amplitude and latency of the MEP are informative about *cortico-spinal excitability* (CSE) of the corticospinal representation of the target muscle (Roesler & Magistris, 2008). MEPs are caused by descending corticospinal volleys that bring spinal motor neurons from the resting state to the firing level. Spinal motor neurons may discharge more than once because of the nature of the descending corticospinal volley which contains a succession of a D-wave (D – direct) and multiple I-waves (I – indirect) converging upon spinal motor neuron (Roesler & Magistris, 2008). D-waves are most likely due to direct activation of the axons of fast pyramidal tract neurons. I-waves are caused by indirect, transsynaptic activation of the corticospinal tract, most likely, by excitatory intra-cortical neurons which synapse onto pyramidal neurons (Roesler & Magistris, 2008). Typically, there are one to four I-waves (I1 – I4-wave). Higher intensity stimulation causes more I-waves, with higher amplitude, with an inter-peak interval of 1.4ms (Roesler & Magistris, 2008). Multiple I-waves are most likely due to activation of the pyramidal tract neurons by a chain of cortical excitatory interneurons. Thus, the MEP, measured by surface EMG over the target muscle, is a summation of the D- and I-waves and reflects, as such, excitability of excitatory interneurons, pyramidal tract neurons, and spinal motor neurons.

To assess the contribution of changes in excitability of spinal motor neurons to the MEP, one can compare changes in MEP evoked by single pulse TMS to the EMG signature of *Hoffmann's reflex* (H-reflex). The H-reflex is an analogue of the stretch reflex and is evoked by electrical stimulation of sensory fibres, more specifically, Ia-afferents stemming from muscle spindles. The H-reflex recruits predominantly small spinal motor neurons. As such, any changes in the H-reflex are informative about changes in spinal excitability. If there are no changes in spinal excitability while MEP size has changed, then the origin of the latter is exclusively cortical.

Using TMS to measure intra-cortical inhibition

Paired-pulse TMS protocols allow non-invasive study of excitatory and inhibitory intra-cortical circuits in M1 (for a review, see Chen, 2004). There are a number of distinct paired-pulse protocols probing short and long intra-cortical inhibition (SICI, LICI), as well as (short) intra-cortical facilitation (SICF, ICF). We here concentrate on SICI and LICI, which are, by far the most heavily studied intra-cortical circuits in M1. SICI is measured by giving two pulses over the same area through one TMS coil with an *inter-pulse-interval* of 1-5ms (Kujirai et al., 1993). The first pulse is given at 70-80% and the second pulse above rMT. SICI leads to a 50-90% reduction of MEP amplitude primarily due to a reduction of later I-waves (I2 - I4). Most likely, SICI is generated by synaptic inhibitory mechanisms at the level of local interneurons in close proximity to the corticospinal neurons of the target muscle in M1. Pharmacological studies have revealed that SICI relies crucially on $GABA_A$ receptor driven neurotransmission (GABA: γ-aminobutric acid; Florian, Müller-Dahlhaus, Liu, & Ziemann, 2008). $GABA_A$ receptors are ligand-gated ion channels with a comparatively fast response (Connors, Malenka, & Silva, 1988; McCormick, 1989; McCormick & Williamson, 1989), consistent with the comparatively short duration of SICI (< 20ms).

By contrast, long intra-cortical inhibition (LICI) acts over a much longer time scale (< 200ms; Connors et al., 1988; McCormick, 1989; McCormick & Williamson, 1989). LICI is measured by giving two TMS pulses above rMT with an interpulse interval ranging from 50 to 200ms. LICI leads to a significant reduction of MEP amplitude primarily due to a reduction of later I-waves (I2 - I4). LICI is mediated by $GABA_B$ receptor driven neurotransmission (McDonnell, Orekhov, & Ziemann, 2006). These receptors are G-protein coupled receptors with a comparatively slow response (Sakaba & Neher, 2003).

The different time course and pharmacological profile of SICI and LICI suggest that these two types of intra-cortical inhibition are mediated by two distinct populations of inhibitory interneurons (Di Lazzaro et al., 2005, 2007; Di Lazzaro et al., 2006). Nevertheless, SICI and LICI interact: at rest LICI inhibits SICI, possibly pre-synaptically via $GABA_B$ receptor mediated transmission (Cash et al. 2010; Chu et al. 2008; Florian et al. 2008; Sanger et al. 2001). Such interactions can be studied by combining paired-pulse protocols to activate both intra-cortical circuits simultaneously. In this case, the SICI protocol is preceded by a TMS pulse above rMT with the inter-pulse interval characteristic for LICI (50-100ms).

SICI, and LICI, as well as SICF, and ICF may all contribute to overt (motor) behaviour, for example, the preparation for action under conditions of event and temporal uncertainty. The functional relevance of distinct excitatory and inhibitory circuits, however, is not yet clear. MEP amplitude increases in the target muscle shortly before motor action (Mars, Bestmann, Rothwell, & Haggard, 2007) while SICI decreases (Reynolds & Ashby, 1999; Soto, Valls-Sole, & Kumru, 2010), consistent with the proposal that SICI sub-serves volitional inhibition of action (Sohn, Wiltz, & Hallett, 2002). The first finding reflects an increasing recruitment of motor neurons underlying forthcoming motor action, whereas the latter reveals that inhibitory processes may regulate the timing of forthcoming motor response by ‘keeping the breaks on’ until it is time to move (Floeter & Rothwell, 1999). Previous studies on the time-course of CSE prior to imperative signals during the preparatory period suggest that there are multiple excitatory and inhibitory processes that underlie preparation for event and temporal preparation (Duque et al., 2005; Duque & Ivry, 2009; Duque, Lew, Mazzocchio, Olivier, & Ivry, 2010).

Functional relevance of inhibitory & excitatory circuits for action preparation

CSE changes throughout the preparatory period prior to imperative events. These changes in excitability suggest that two (Davranche et al., 2007; Duque et al., 2010), possibly three (Hasbroucq, Kaneko, Akamatsu, & Possamaï, 1997, 1999; Hasbroucq, Osman, et al., 1999), processes may underlie preparation for imperative events and motor action. First, selection, preparation, and successful execution of motor action may be implemented by a relative increase in CSE in the corticospinal representation of the selected and thus prepared action (*response competition*; Bestmann et al., 2008; Cisek, 2006, 2007; Cisek & Kalaska, 2005, 2010; Duque et al., 2010; Michelet, Duncan, & Cisek, 2010). This relative difference in CSE for the prepared versus unprepared action may be due to either an increase in CSE for the prepared action (van Elswijk, Kleine, Overeem, & Stegeman, 2007) or a decrease in CSE for the unprepared alternative (Duque & Ivry, 2009), or both. Second, during preparation for action, an adaptive mechanism may selectively suppress neural excitability for the prepared action to prevent premature responses *before* the imperative event (*impulse control*; Duque & Ivry, 2009; Duque et al., 2010; Floeter & Rothwell, 1999). Third, an adaptive mechanism may prepare the corticospinal representation of the selected action to receive and implement the voluntary motor command by decreasing its background noise (i.e. task-unrelated afferents; *noise reduction*) leading to an overall decrease in CSE for the prepared action (Burle, Bonnet, Vidal, Possamaï, & Hasbroucq, 2002; Hasbroucq et al., 1997; Hasbroucq, Kaneko, et al., 1999; Hasbroucq, Osman, et al., 1999).

While these three accounts link changes in CSE to preparatory processes in anticipation of the imperative event (and the ensuing motor response), changes in

CSE prior to the imperative event may also be due to processes *unrelated* to the imperative event and ensuing motor action. The warning stimulus, for example, may trigger (sub-threshold) motor activity (Boulinguez, Jaffard, Granjon, & Benraiss, 2008), which, in turn, may cause a transient increase in CSE for the instructed action. This highlights the potential functional relevance of a putative process that suppresses responses to non-imperative events. This process may act when the imperative event is less likely to happen. As such, this process could contribute critically to temporal preparation. Further, gradual changes in CSE throughout the preparatory period may reflect processes that underlie 'keeping track of time' (Janssen & Shadlen, 2005; Leon & Shadlen, 2003; Mita et al., 2009) which may not be directly related to temporal or event preparation. Fixed or constant foreperiod (FP) designs (Hasbroucq et al., 1997; Hasbroucq, Kaneko, et al., 1999; Hasbroucq, Osman, et al., 1999), or variable FP designs when the time of the TMS is locked to the warning stimulus (i.e. constant delay between warning stimulus and TMS), are particularly vulnerable to these two alternative explanations for changes in CSE throughout the preparatory period. In chapter 4, we explore whether changes in CSE can be described best by response competition, impulse control, or noise reduction by removing ETU and ITU (Experiment 1) or targeted manipulation of ETU (Experiment 2). We further aim to exclude non-motor explanations for changes in CSE during preparation for action.

Chapter 5 present an experiment that aims to further elucidate the functional role of SICI and LICI in preparation for action. CSE is shaped by intra- and inter-cortical excitatory and inhibitory circuits that increase or decrease CSE, respectively. Thus, distinct inhibitory or excitatory intra-cortical circuits may have functional significance in preparation for action, supporting either *response competition*, *impulse control*, or, *noise reduction*. Recent studies have reported decreasing CSE during the preparatory period, which highlights the importance of inhibitory processes during preparation for action (Davranche et al., 2007; Duque & Ivry, 2009; Duque et al., 2010; Hasbroucq et al., 1997; Hasbroucq, Kaneko, et al., 1999; Hasbroucq, Osman, et al., 1999; Soto et al., 2010); although a decrease in CSE may also be caused by a removal of excitation (i.e. disinhibition). SICI and LICI, for example, may contribute to the time-course of CSE during preparation for action. However, the functional significance of SICI, and in particular LICI, during selection and preparation for action remains unclear. The different time courses of $GABA_A$ and $GABA_B$ receptor mediated intra-cortical inhibition suggest that LICI and SICI may play different functional roles (Chen, 2004). SICI could take on a functional role that requires high temporal precision, such as preventing the premature release of prepared action (impulse control; Floeter and Rothwell 1999; Hasbroucq et al. 1997, 1999; Reynolds and Ashby 1999) due to the fast response of $GABA_AR$. LICI on the other hand could contribute to the prevention of responses to non-imperative stimuli, as this form of inhibition needs to be maintained tonically to prevent unwanted actions to non-imperative stimuli. Alternatively, LICI could prevent the execution of non-selected action alternatives tonically suppressing their neural representations (contributing to *response competition*). The comparatively slow response of $GABA_BR$ makes LICI a good candidate for taking on one of these two functional roles that require tonic suppression.

ETU and ITU in reward-based decision making

Uncertainty or advance information about future events should also affect decisions about which action alternative to commit to, in particular when expected reward decreases with increasing uncertainty. Consider jumping from one boat to another in a choppy sea. The key factors that should affect your choice are your probability of success and the costs and benefits you anticipate as consequences of success and failure (ruining your clothes, exciting laughter, etc.). Your probability of success depends on both the *external* erratic movements of the boat and your own *internal* motor uncertainty (i.e. how good you are at jumping). In deciding whether to jump or not, both types of uncertainty need to be taken into account as they have equivalent effects on outcome: it makes little difference whether your woeful state, in case of failure, resulted from an unexpected lurch by the boat or a particularly maladroit jump. Combining uncertainty from external and internal sources to estimate the expected costs and benefits is a key challenge in deciding between alternative actions. In chapter 6, we examine the ability to estimate and combine ETU and ITU in a reward-based decision making task that puts a premium on the accurate timing of motor actions.

For the most part, previous studies on decision making have focused on the effects of either external or internal uncertainty on reward-based decision-making. The scientific study on the effects of *external* risk and uncertainty on choice has a long-standing tradition in psychology and economics (Allais, 1953; Friedman & Savage, 1948; Kahneman & Tversky, 1979; Kahneman & Tversky, 2000; Lichtenstein, Slovic, Fischhoff, Layman, & Combs, 1978; Tversky & Kahneman, 1992). Further, the neural mechanisms underlying choice under external risk and uncertainty have received much attention in recent years (Daw, Niv, & Dayan, 2005; Dayan & Daw, 2008; De Martino, Kumaran, Seymour, & Dolan, 2006; Rushworth, Noonan, Boorman, Walton, & Behrens, 2011; Trepel, Fox, & Poldrack, 2005). Typically, participants exhibit patterned deviations from optimal performance in the face of external uncertainty. For example, participants overestimate the probability of infrequent events and display risk aversion (Tversky & Kahneman, 1992).

Perception and action, however, are intrinsically uncertain, too (Bays & Wolpert, 2007; Wolpert, 2007). Visuo-motor decision tasks ("motor lotteries") and economic decision tasks can be translated into a common mathematical language (i.e. statistical decision theory), which allows comparison of performance under external and internal uncertainty (Trommershäuser, Maloney, & Landy, 2003, 2008). In these tasks, participants typically, but not always (Trommershäuser, 2009), select actions that take into account their own visual and motor uncertainties and come close to maximizing expected reward (Gepshtein, Seydell, & Trommershäuser, 2007; Seydell, McCann, Trommershäuser, & Knill, 2008; Trommershäuser, Gepshtein, Maloney, Landy, & Banks, 2005; Trommershäuser, Landy, & Maloney, 2006).

Patterned deviation in choice under conditions of external but not internal uncertainty suggests a fundamental difference between these two types of uncertainty. In Chapter 6, an experiment is presented which looks at choice under conditions of ETU and ITU to elucidate the possible differences.

Reducing ITU through integration of multiple cues

Performance often relies on the accurate perception of time. An accurate estimate of the “go-signal” improves a sprinters performance. ITU limits accuracy of time estimates. So far, we have treated ITU as a quantity that may or may not interfere with temporal expectation and preparation, or reduce expected outcome, unless it is reduced or removed by accurate external clocks. Participants may use other strategies, though, in the absence of accurate external clocks, to reduce ITU. Multiple cues may be informative about the appropriate time for action. Participants may combine this information provided by multiple cues to reduce ITU, a phenomenon typically known as “cue combination” or “cue integration”.

There are many examples of successful cue integration in the literature. Integration of visual and haptic information improves depth perception (Ernst & Banks, 2002; Girshick & Banks, 2009; Hillis, Ernst, Banks, & Landy, 2002; Hillis, Watt, Landy, & Banks, 2004; Johnston, Cumming, & Landy, 1994; Knill, 2007; Knill & Saunders, 2003). Localization of one’s own limbs (Sober & Sabes, 2005; van Beers, Wolpert, & Haggard, 2002), or entire body (Fetsch, DeAngelis, & Angelaki, 2010; Fetsch, Turner, DeAngelis, & Angelaki, 2009) improves through the integration of visual and proprioceptive information. Finally, motor performance improves through the integration of visual and proprioceptive information with the efference copy, a prediction about the sensorimotor consequences of motor actions (Bays & Wolpert, 2007; van Beers, Baraduc, & Wolpert, 2002; Wolpert, 2007). In the final chapter, we explore whether participants can combine temporal information from multiple cues to reduce ITU and improve their timing performance.

Taken together, this thesis presents a series of studies that explore the effects of ETU and ITU on temporal expectation and preparation, including neurophysiological correlates, and reward-based choice. Finally, we address a possibility to reduce ITU by integrating multiple cues all informative about action timing. As such, this thesis (re-)introduces two types of temporal uncertainty, ETU and ITU, largely overlooked since introduced by Klemmer (Klemmer, 1956, 1957). The studies presented here reveal distinct effects of ETU and ITU on temporal expectation and preparation, their neural underpinnings, and reward-based choice, highlighting the importance of the distinction between ETU and ITU for empirical research on explicit and implicit timing in the interval timing range. In short, the *origin* of uncertainty matters for a wide range of behaviour.

Chapter 2: The effects of external and internal temporal uncertainty on preparation for action

Preparation for imperative events relies on accurate estimates about their time of occurrence. The accuracy of such estimates is limited by variability of events in time (ETU: External Temporal Uncertainty) and our limited capacity to measure time accurately (ITU: Internal Temporal Uncertainty). In a series of three experiments, we asked how these two types of temporal uncertainty interact, whether they can be dissociated from one another, and whether their effects arise from strategic adjustments in action preparation or automatic conditioning processes. Participants performed a modified implicit perceptual timing task with variable foreperiod (FPs) durations. ETU and ITU were manipulated in a factorial fashion (Experiment 1). In Experiment 2 reliable information about the passage of time removed ITU. In Experiment 3, information about the timing of the imperative event removed ETU in addition to ITU. Our results demonstrate that overall preparation (mean RT) and consistency in preparation (variability in RT) are affected by both ETU and ITU. While participants benefit from low ETU, high ITU can mask these beneficial effects. Sequential effects – the effect of the duration of the foreperiod of a preceding trial on current reaction time – are stronger for high levels of ETU. Removal of both ETU and ITU abolishes sequential effects. The strength of the FP effect increases with high ETU but decreases under conditions of high ITU. Again, removal of ETU and ITU abolishes the FP effect. Results thus support strategic accounts on temporal processing: explicit and reliable information about the timing of the imperative event removes effects of ETU and ITU. Further, ETU and ITU have distinct effects on temporal preparation. Two distinct processes may be concerned with the estimation of ETU and ITU and differentially affect preparation for action in an (temporally) uncertainty world.

Keywords: action preparation, implicit timing, external temporal uncertainty, internal temporal uncertainty, temporal orienting, foreperiod paradigm, temporal expectation

Time is a fundamental dimension of motor planning and performance (Woodrow, 1914). In many situations, temporal uncertainty limits the accuracy with which one can predict the timing of future imperative events, often with detrimental effects on behavioural performance. Accuracy is limited by both variability of events in time (ETU: External Temporal Uncertainty) and our limited capacity to measure time accurately (ITU: Internal Temporal Uncertainty). ETU and ITU are both likely to influence motor planning and performance (Klemmer, 1956, 1957), yet little is known about the specific effects of these two types of temporal uncertainty on preparation for action: whether they interact, and how possible interaction may affect the time course of action preparation. Crucially, the fundamentally different nature of these two sources of temporal uncertainty suggests differential effects on behaviour.

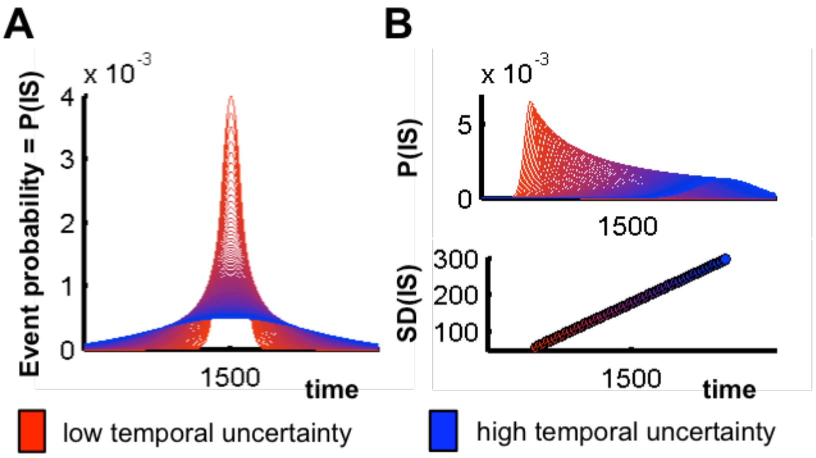


Figure 2.1: External (ETU) and internal (ITU) temporal uncertainty. A. ETU (left) is induced by variability in the timing of imperative events. With increasing variability, their timing is harder to predict, which leads to higher levels of ETU. **B.** ITU (right) is induced by noisy internal clocks. Internal temporal noise increases with longer to-be-estimated time intervals, which leads to higher standard deviation in time interval estimates centred on their true duration (right bottom graph). The level of ITU therefore increases with increasing time interval duration.

In a series of three experiments, we here asked how these two types of temporal uncertainty influence action preparation using a variable foreperiod (FP) simple reaction time task (Niemi & Naatanen, 1981). We specifically assessed how ETU and ITU affect the hallmark features of implicit timing: the foreperiod effect (Bueti et al., 2010; Jean Requin & Granjon, 1969) and sequential effects (S. Los et al., 2001). The foreperiod effect may reflect either strategic adjustments in preparation that mirror the increase in the probability of the imperative event with elapsed foreperiod duration (i.e. the hazard function; Nobre, Correa, & Coull, 2007; Requin & Granjon, 1969) or emerge as a side-effect of the sequential effects. Sequential effects are either due to strategic and dynamic adjustments in preparation due to an expectation of foreperiod repetition with ensuing re-preparation if the imperative event occurs later than expected (Drazin, 1961) or emerge from trace-conditioning (Los et al., 2001). Trace conditioning explains sequential effects as a consequence of automatic adjustments in preparation.

Previous studies have focused either on the effects of ITU in constant FP paradigms (P Bertelson, 1967), or on the effects of combined ETU and ITU in variable FP paradigms (P Bertelson & Tisseyre, 1968; Bueti et al., 2010; S. Los et al., 2001; S. Los & Schut, 2008). Crucially, no study to date has yet studied and directly compared how temporal preparation is shaped by ETU and ITU, respectively. We investigated how ETU and ITU shape temporal preparation using a factorial design in which we varied the degree of ETU and ITU independently. Moreover, in separate experiments, we explicitly removed ITU, or both ITU and ETU. The latter allowed us to test the predictions made by the strategic versus (trace) conditioning account of temporal preparation. The conditioning account predicts residual effects of ETU and ITU even if both are removed by explicit accurate information (S A Los & van den Heuvel, 2001; S. Los & Heslenfeld, 2005). The strategic accounts, by contrast, do not predict such residual effects under conditions of full advance information about the timing of the imperative event (Jean Requin & Granjon, 1969). Removal of ITU, by contrast, allows for studying the effects of ETU in isolation.

We specifically focused on the impact of ETU and ITU on average response times, their variability, and how ETU and ITU modulate the FP and sequential effects. The latter two are of particular interest because they can reveal the specific processes through which these two types of temporal uncertainty modulate preparation and provide evidence in support of the aforementioned strategic versus conditioning accounts of temporal preparation.

In all three experiments, we manipulated FP variability and mean duration. In *Experiment 1*, participants did not receive advance information about the timing of the imperative events. Consequently they experienced both ETU, due to FP variability, and ITU, due to having to keep track of the passage of time. We expected beneficial effects of low ETU and low ITU on action preparation – the less overall temporal uncertainty, the better our ability to anticipate and prepare for imperative events. Moreover, we also expected that high ITU might interfere with learning of temporal predictability of imperative events and might therefore reduce beneficial effects of low ETU. For similar reasons, we predicted an attenuation of the FP effect for high ITU, whereas ETU should not significantly alter the FP effect. Both the strategic account and the conditioning account predict an attenuation of sequential effects under conditions of high ITU, because ITU limits the precision with which participants can prepare for the anticipated FP repetition.

In *Experiment 2,* we asked whether the effects of ITU can be selectively removed by providing participants with reliable information about the passage of time (Borst & Cohen, 1987) whilst preserving inter-trial differences in mean FP duration. Successful removal of the effects of ITU on action preparation would suggest that the processes underlying these effects are (a) under cognitive control and (b) fully dissociable from processes underlying the effects of ETU.

In *Experiment 3*, we asked whether the combined effects of ETU and ITU are under cognitive control. We removed both ETU and ITU by providing continuous information about the passage of time and the exact time of occurrence of the IS (Borst & Cohen, 1987; Carlsen & Mackinnon, 2010) whilst preserving differences in mean FP duration and variability. Siding with the strategic account and assuming cognitive control, we expected this removal to abolish the FP effect and sequential effects.

Methods

Participants

47 participants (10 male, 2 left-handed; mean age 23.8 years, range: 18-45 years) with normal or corrected-to-normal vision took part in this study (Experiment 1: N = 18, Experiment 2: N = 15, Experiment 3: N = 14). Participants were recruited via the participants' database of the Department of Psychology of University College London and reimbursed for time and travel (£7.50/h). Before participation,

participants gave written informed consent. This study was conducted with the approval of a local ethics committee and in line with the declaration of Helsinki.

Apparatus

The experiment was run on a desktop computer, using the cogent 2000 toolbox (http://www.vislab.ucl.ac.uk/cogent.php) running under Matlab 8.5 (Mathworks, Natick, MA). Stimuli were presented on a 19' LCD screen with a refresh rate of 60Hz. Participants sat in a reclining chair 40 cm in front of the screen and responded by pressing the V-key and M-key with their left and right index finger, respectively, on a standard QWERTY keyboard. Throughout the experiment, participants wore headphones. They received an auditory stimulus of 50 ms at 400 Hz (60 dB) as error feedback (see below). All visual stimuli subtended approximately 5 degrees of visual angle.

Experimental procedure & design

Participants completed a variable FP simple reaction time task. They were instructed to respond to the appearance of an imperative stimulus (IS) as fast as possible but not at the expense of accuracy (Figure 2.1). FPs were sampled from continuous truncated normal distributions. We manipulated mean FP duration (mean = 1500 / 3000ms) and FP variability (standard deviation = 100 / 600ms). By increasing mean FP duration, one can manipulate ITU (unless one uses special measures to remove ITU, see description of Experiment 2) because accuracy of time interval estimation decreases in direct proportion to time interval duration (J Gibbon, 1977). Higher FP variability increases ETU by increasing the variability in the timing of IS occurrence (unless ETU is removed otherwise, see description of Experiment 3).

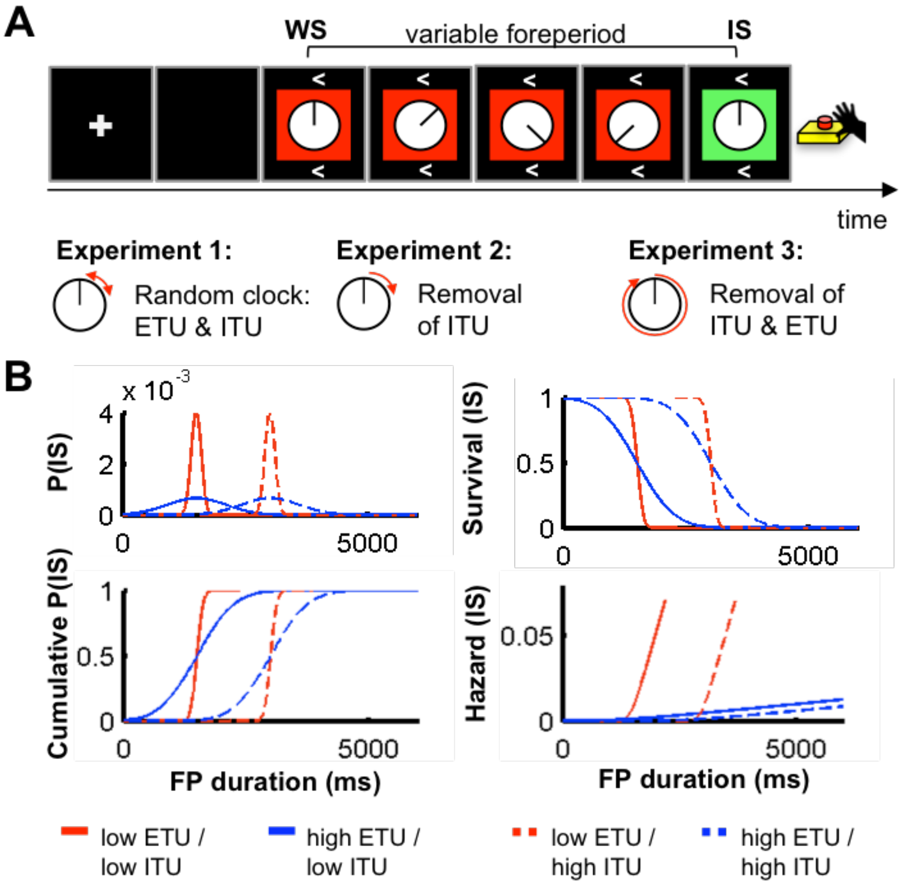


Figure 2.2: Modified variable foreperiod reaction time task. A. Trials started with presentation of a fixation cross (200 ms). After a blank screen (300 ms), participants were presented with a simple clock superimposed on a red square. Appearance of the clock served as the warning stimulus (WS). The clock hand started turning upon presentation. Arrows above and below the clock instructed the response (left or right hand button press). After a variable foreperiod (FP), the red square changed colour to green, which provided the imperative stimulus (IS) that prompted participants to respond as quickly as possible with the instructed finger. The WS provided an endogenous temporal cue, whereas the FP duration of the previous trial served as an exogenous cue. The time since trial onset determines the conditional probability of IS occurrence (hazard function). In Experiment 1 the clock started at the 6 o'clock position and moved back and forth in a random walk. It therefore did not provide reliable information about the passage of time. In Experiment 2, the clock hand started at the 12 o'clock position and completed one full rotation. This provided reliable information about the passage of time thus removing ITU. In Experiment 3, the clock hand started in the 12 o'clock position and completed one full rotation. The return to the 12 o'clock position coincided with presentation of the IS. This provided explicit and reliable information about the time of IS occurrence, and therefore removed both ETU and ITU. **B.** Foreperiods (FPs) were sampled from continuous Gaussian distributions (top left, see probability density function), where the mean manipulated ITU (1500 / 3000ms) and the standard deviation manipulated ETU (100 / 600ms). The bottom left graph shows the cumulative Gaussian distributions, the top right the survival function and bottom right the hazard rate. The hazard rate is the ratio of the probability density function to the survival function. The hazard rate of the imperative stimulus (IS) increases progressively with the passage of time. Note the earlier rise in conditional probability for low ITU, and the steeper slope for low ETU.

For short mean FP durations (1500 ms), the normal distribution was truncated at 500ms, which has been suggested as the minimum time required for preparation (Hackley, 2009; Hackley et al., 2009). Truncation at 2500ms (max. FP duration) preserved the symmetry of the normal distribution (Figure 2.2). To ensure comparable standard deviations for short and long mean FP duration, the same was done for the long mean FP duration (3000ms) condition. In this case, we truncated the normal distribution at 2000ms and 4000ms, respectively.

Each trial started with presentation of a fixation cross for 200ms (Figure 2.1). After a delay of 300ms, participants saw an analogue clock, comprised of a white circle with a black clock hand. This clock was presented at the centre of the screen, superimposed on a red square. The clock hand started moving upon presentation. Above and below the clock were two arrows, which pointed either towards the left (50% of all trials) or towards the right. These arrows instructed the response (left / right button press) that was required at IS appearance, which was signalled by a change in colour of the central square from red to green. Inter-trial intervals were sampled from a non-ageing (exponential) distribution (mean = 500ms). 500ms were added to every sampled inter-trial interval.

Prior to each experiment, participants completed a training session of 40 trials to familiarise themselves with the experiment. During training, participants received feedback whenever they made an error. Errors were of four types: (a) a premature response, (b) a slow response, more than 500ms after IS occurrence, (c) a response omission, or (d) an incorrect button press (i.e. left when instructed to press right). In case of incorrect responses, written feedback was displayed on the screen informing participants about the type of error they had made. In case of premature responses, participants heard a short warning tone (50ms) in addition. FPs for the training were sampled from a non-ageing (exponential) distribution with a mean of 1000ms. 300ms were added to every sampled delay. Any delay lower than 500ms was re-sampled from the exponential distribution. We used this distribution during training to prevent participants from familiarising themselves with the specific distributions and the associated changes in hazard rate over the course of a trial that they would later experience during the main experiment.

In all experiments, participants completed four blocks of 120 trials, one block for each experimental condition in our 2 x 2 factorial design. Participants took breaks every 40 trials within a block, and after completion of each block. During the experiment, participants did not receive trial-by-trial error feedback with the exception of the tone in case of premature responses. Instead, they received summary feedback every 20 trials. Feedback about the number of late response (reaction time > 500ms) and response omissions (> 1000ms) was given to encourage preparation and faster responses.

Experiment 1: action preparation under conditions of ITU and ETU

In Experiment 1, the clock hand moved forwards and backwards in a random walk, starting at the 6 o'clock position. Therefore, no information about the passage of time or the time of occurrence of the IS was conveyed by the clock. The speed of the clock hand was adjusted to the mean FP duration in that block. We included the clock in Experiment 1 to ensure comparable stimulus characteristics across experiments (see below). A separate control experiment (data not reported here) verified that changes in clock speed, which here co-varied with ITU, cannot explain the effects of ITU reported below.

Experiment 2: action preparation under conditions of ETU, when ITU is removed

In experiment 2, the clock hand completed one full rotation on average, starting at the 12 o'clock position, with the speed of the clock hand adjusted to the mean FP duration of a block. This provided constant feedback about the passage of time, and therefore removed participants' ITU whilst preserving differences in mean FP duration between conditions. Therefore, the factor ITU reduces to *mean FP duration* (meanFP) because the passage of time was not explicitly communicated to the participants. In other words, an accurate clock removed all ITU. But the clock did not allow for predicting the time of IS occurrence and therefore did not remove or reduce ETU.

Experiment 3: action preparation in the absence of ETU and ITU

In Experiment 3, the clock hand completed one full rotation on every single trial, starting at the 12 o'clock position, with the speed of the clock hand now adjusted to the duration of the specific FP on each trial. This provided continuous and reliable information about both the passage of time and the time of occurrence of the IS (return to the 12 o'clock position). Therefore, the factor ETU reduces to *FP variability* (FPvar), because subjects could fully predict when the IS would occur. The factor ITU reduces to *mean FP duration* (meanFP) because subjects were fully aware about the passage of time. In short, we removed ITU and ETU, whilst preserving differences in FP variability and mean FP duration between conditions.

Data analyses

Reaction time (RT) was defined as the time between the onset of the IS and the behavioural response. Responses were considered correct if the response was made after the presentation of the IS with the instructed finger. All trials with incorrect responses were excluded from the RT analyses. In addition, we excluded outliers in RTs (Grubb's test, $\alpha = 0.05$). Finally, participants with an overall error rate exceeding 20% of all trials were excluded from further analyses. In all analyses, RTs were averaged across left (50%) and right hand responses (50%).

RT data were analysed in three different ways. Each analysis was aimed at exploring specific effects of ETU and ITU on preparation. First, we analysed how ETU and ITU influence how quickly and consistently participants responded to the IS. Second, we studied sequential effects under ETU and ITU, that is, the effect of the foreperiod of the preceding trial on current RTs. Third, we explored the effects of ETU and ITU on the FP effect, that is, how reaction times change depending on current foreperiod duration.

For all analyses, we report partial η_p^2 as a measure of effect size. Significant interaction effects were followed-up using paired t-tests. Statistical threshold was fixed at $\alpha = 0.05$ and, whenever appropriate, corrected for multiple comparisons using Bonferroni correction. Greenhaus-Geisser correction was applied to degrees of freedom whenever significant Mauchly's test signalled violation of sphericity.

Analysis of reaction times and their variability

To analyse distribution, central tendency, and consistency of participants' RTs, we first constructed the cumulative frequency distribution of RTs for each participant separately and then fitted a sigmoid function to this distribution. A good fit of the sigmoid to the data suggests unimodally distributed RT data. The mid-point and slope provide convenient measures of central tendency and consistency (i.e. variability) in RTs, respectively.

To construct the cumulative frequency distribution, we determined the size of the smallest data-set in the sample ($N_{min(data\text{-}set)}$). Data-set was defined as all data-points in one experimental condition for one participant. Due to exclusion of errors, the size of data-sets differed across conditions and participants. To match data-sets in sample size, we *randomly* selected $N_{min(data\text{-}set)}$ data-points from all data-sets that contained more data-points than the smallest data-set (see also (Bertelson & Barzeele, 1965; Hohle, 1965). Subsequently, we assigned ranks to all RTs for each data-set separately, and sorted RTs according to their rank to obtain the cumulative frequency reaction time distribution for each experimental condition and participant separately (Bertelson & Barzeele, 1965; Hohle, 1965). As a consequence of matching data-sets in sample size, the upper and lower bound of these cumulative frequency distributions were identical across data-sets (=$N_{\text{min(data-set)}}$) and each rank had the same "meaning". For example, if $N_{\text{min(data-set)}} = 96$ then the 48th reaction time constituted the median reaction time for each participants and condition.

We then fitted sigmoid functions to these cumulative frequency RT distributions separately for each participant and experimental condition. As the estimated mid-point or slope may be biased by random selection of extreme RT values (which may or may not have been included when randomly selecting trials to match data-sets in sample size), we repeated our procedure 10.000 times and computed mid-point and the slope averaged across these repetitions.

We then ran two 2 x 2 within-subject repeated measures ANOVAs on the average mid-point and slope with ITU and ETU as factors. Goodness of fit (R^2-adjusted), averaged across repetitions, was inspected to confirm that the data were unimodally distributed and indeed appropriately modelled by sigmoid functions.

Analysis of sequential effects

We tested for the effect of ITU and ETU on sequential effects. First, we standardised FP duration for each combination of ITU and ETU by subtracting the mean FP duration from sampled FPs and then dividing this difference by the standard deviation in FPs. This accounts for (experimentally manipulated) differences in mean FP and FP variability. Second, we created three equally spaced bins [-2, 0, +2] of standardised FP duration, and assigned each trial to one of these bins depending on the current trial's FP duration and the immediately preceding trial's FP duration. We chose three bins to ensure a sufficiently high number of trials in each experimental condition defined by the current and preceding trial's FP duration (12.7 trials on average). We then classified the data according to the nine combinations of the FP of the current trial (FP_n; short, intermediate, long) and the FP of the preceding trial (FP_{n-1}; short, intermediate, long). Third, we computed the mean reaction time for each experimental condition defined by the current and previous trial's FP separately for each combination of ETU and ITU.

We assessed the influence of temporal uncertainty on sequential effects in a 3 x 3 x 2 x 2 within-subject repeated-measures ANOVA on mean reaction times with the following repeated measures factors: current FP (FP_n: short, intermediate, long), preceding FP (FP_{n-1}:short, intermediate, long), ETU (low, high), and ITU (low, high). As this analysis was conducted with the specific aim to look at sequential effects: any effect of FP_{n-1}, in particular any interaction between FP_{n-1} and either ETU, ITU, or both, will therefore be of particular interest. While we do report all significant effects of the ANOVA, we focus on the discussion of sequential effects (effects of FP_{n-1}) and their interaction with other factors.

Analysis of the foreperiod (FP) effect

To address how ITU and ETU influence the FP effect, we assessed the relation between FP duration and mean RTs. First, we standardised FPs separately for each experimental condition by subtracting the mean FP from sampled FPs and dividing this difference by the standard deviation in FPs. This procedure accounted for the differences in mean FP duration and FP variability in the experimental conditions. Subsequently, we created nine equally spaced bins of normalised FP duration (ranging from -2 to 2) and computed the average RT for each bin for each experimental condition and participant separately. We chose nine bins to ensure a sufficiently high number of trials in each bin (12.7 trials on average). Our conclusions did not change when using a slightly larger or smaller number of bins.

We fitted linear regression models to mean RTs against normalised FP duration, separately for each experimental condition and participant. During the experiment, FPs were sampled from truncated normal distributions. Consequently, linear regression models should provide a good approximation to the RT data if participants indeed showed evidence for the FP effect, that is, if participants RTs reflect the hazard rate (see Figure 2.1B). We used $R^2_{adjusted}$ as a measure of the goodness of fit. In addition, we extracted the linear regression coefficients, which reflect the change in RT with increasing FP duration. Negative regression coefficients reflect a decrease in RTs with increasing FP duration, as the FP effect would predict. To test for a modulation of the FP effect by ITU and / or ETU, we computed a 2 x 2 repeated-measures ANOVA on regression coefficients with ITU (high, low) and ETU (high, low) as factors. Finally, to test whether regression coefficients reflected a significant RT change with FP duration, we tested regression coefficients against zero using one-sample t-tests.

Results

Effects of ETU and ITU on central tendency and variability in reaction times

Experiment 1: action preparation under conditions of ITU and ETU

6.9% of all trials (4.2% due to premature responses) were excluded from further analysis. The smallest data-set in the sample comprised 95 data-points (= $N_{min(data\text{-}set)}$) after exclusion. The data were unimodally distributed, as revealed by good sigmoid fits and correspondingly high R^2_{adj} (see Table 2.1).

Participants responded significantly faster under conditions of low compared high ITU as revealed by a significant effect of ITU on the mid-point of the fitted sigmoid (*$F_{(1,17)}$ = 5.89, p = 0.027,* η_p^2 *= 0.257*), which here served as a measure of central tendency (Figure 2.3). ETU had no effect on this measure.

The ANOVA on slope by contrast revealed a significant interaction effect between ITU and ETU *($F_{(1,17)}$ = 7.09, p = 0.017,* η_p^2 *= 0.294)*. This interaction effect was driven by higher variability in RTs, expressed by a flattened cumulative RT frequency distribution, for high compared to low ETU but under conditions of low ITU only *($t_{(17)}$ = -2.40, p = 0.028)*. The slope for high and low ETU did not differ significantly under conditions of high ITU (*$t_{(17)}$ = 1.22, p = 0.238*).

Experiment 2: action preparation under conditions of ETU, when ITU is removed

5.0% of all trials (2.0% due to premature responses) were excluded from further analysis. The smallest sample in the dataset comprised 88 data-points (=$N_{min(data\text{-}set)}$) after exclusion. The data were unimodally distributed as revealed by high R^2_{adj} (see Table 2.1).

Participants responded significantly faster under conditions of low compared to high ETU *($F_{(1,14)}$ = 51.56, p < 0.001,* η_p^2 = 0.786*)*. MeanFP by contrast had no effect on reaction times ($F_{(1,14)}$ = 0.55, p = 0.472, η_p^2= 0.037). Also, there was no interaction effect between ETU and meanFP ($F_{(1,14)}$ = 0.38, p = 0.382, η_p^2= 0.055).

The ANOVA on slope revealed higher variability in RT, expressed by a flatter cumulative frequency distribution of RTs, under conditions of high compared to low ETU (*$F_{(1,14)}$ = 10.07, p = 0.007* η_p^2= 0.418; see Figure 2.3). There was no effect of meanFP ($F_{(1,14)}$ = 0.26, p = 0.616, η_p^2= 0.016) and no interaction between ETU and meanFP ($F_{(1,14)}$ = 0.07, p = 0.802, η_p^2 = 0.005).

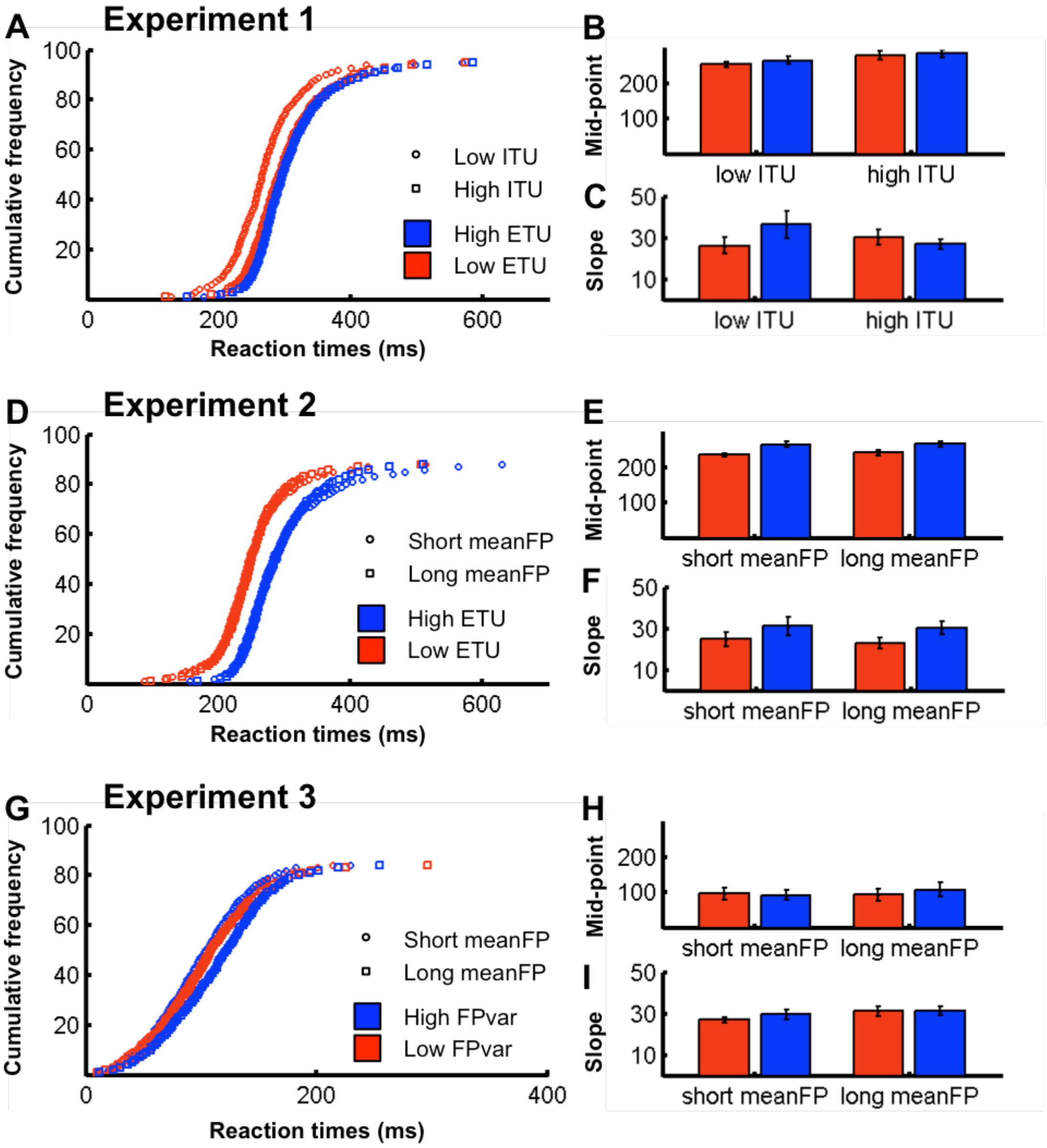


Figure 2.3 Action preparation under conditions of external (ETU) and internal temporal uncertainty (ITU; Experiment 1), ETU and meanFP (Experiment 2), and FPvar and meanFP (Experiment 3). ADG. Sigmoid functions were fitted to cumulative reaction time frequency distributions. These functions provided good fits to the data as revealed by high R^2-adjusted. **BEH.** Average mid-points of sigmoid fits – a measure of central tendency – for each experimental condition and experiment. **B.** *Experiment 1*: higher levels of ITU lead to significantly higher mid-points thus revealing on average slower responses for high ITU. **E.** *Experiment 2*: high levels of ETU lead to slower responses for both short and long meanFP, while the effect of meanFP (ITU) disappeared. **H.** *Experiment 3*: no significant effects of meanFP and FPvar. **CFI.** Average slope of sigmoid fits – a measure of dispersion – for each experimental condition and experiment. **C.** *Experiment 1*: we found an increase in slope for high levels of ETU only when ITU was low. **F.** *Experiment 2*: we found an increase in slope for high ETU for both short and long meanFP. **I.** *Experiment 3*: No significant effects of meanFP and FPvar. Errorbars reflect standard error.

Experiment 3: action preparation in the absence of ETU and ITU

3 subjects were excluded from the analysis as their overall error rate exceeded 20%, primarily due to premature responses. In addition 9.1% of all trials, 6.6% due to premature responses, were omitted from further analysis. The smallest data-set in the sample comprised 84 data-points (= $N_{\text{min(data-set)}}$) after exclusion. Inspection of R^2_{adj} revealed that the data were unimodally distributed (Table 1). ANOVAs on mid-point and slope of fitted sigmoid functions did not reveal any significant effects of meanFP and FPvar.

Taken together, explicit information about the timing of the IS removes any effects of mean foreperiod duration as well as foreperiod variability (Experiment 3). When participants are provided with an accurate external clock that removes ITU (Experiment 2), then low levels of ETU benefits performance both by decreasing the average time taken to respond and by increasing consistency in RTs. Under conditions of ETU *and* ITU, effects of ETU on the average time taken to respond disappear, probably masked by even relatively low levels of ITU. Further, the effects of ETU on reaction time variability are apparent only when ITU is low. In short, ITU affects how participants cope with ETU.

Table 2.1: Goodness-of-fit for sigmoid functions (analysis of central tendency and variability in reaction times) and linear regression models (analysis of FP effect). Sigmoid functions provided good fits to the cumulative reaction time frequency distributions for all 4 experimental conditions. RT data were thus unimodally distributed. The linear regression explains a weak to moderate proportion of the reaction time data against FP duration.

Experiment	Analysis	Parameter	Condition			
			Low ITU		High ITU	
			Low ETU	High ETU	Low ETU	High ETU
1	**Sigmoid fits**	R^2 **adjusted**	0.99 (SE = 0.001)	0.99 (SE = 0.001)	0.99 (SE = 0.001)	0.99 (SE = 0.001)
	FP effect	R^2	0.23 (SE = 0.06)	0.57 (SE = 0.06)	0.18 (SE = 0.05)	0.40 (SE = 0.07)
2	**Sigmoid fits**	R^2 **adjusted**	0.99 (SE = 0.001)	0.99 (SE = 0.001)	0.99 (SE = 0.001)	0.99 (SE = 0.001)
	FP effect	R^2	0.40 (SE = 0.07)	0.50 (SE = 0.06)	0.31 (SE = 0.07)	0.34 (SE = 0.05)
3	**Sigmoid fits**	R^2 **adjusted**	0.99 (SE = 0.001)	0.99 (SE = 0.001)	0.99 (SE = 0.001)	0.99 (SE = 0.001)
	FP effect	R^2	0.14 (SE = 0.04)	0.25 (SE = 0.08)	0.21 (SE = 0.06)	0.29 (SE = 0.07)

Sequential effects

Experiment 1: action preparation under conditions of ITU and ETU

The ANOVA for repeated measures revealed significant main effects of ITU ($F_{(1,17)}$ = 9.30, p = 0.006, η_p^2 = 0.369) and ETU ($F_{(1,17)}$ = 10.01, p = 0.006, η_p^2 = 0.370; see Figure 2.4). In addition, there was a significant interaction effect between ETU and ITU ($F_{(1,17)}$ = 6.11, p = 0.024, η_p^2 = 0.264). Under conditions of low ITU, responses were faster for low compared to high ETU ($t_{(17)}$ = -3.91, p = 0.001). There was no difference under conditions of high ITU between low and high ETU ($t_{(17)}$ = -0.83, p = 0.421).

Current FP duration (FP_n) had a significant effect on mean RTs ($F_{(2,34)}$ = 45.22, p < 0.001, η_p^2 = 0.727). The effect of the previous FP duration (FP_{n-1}) on RT of the current trial was marginally significant ($F_{(1.40,23.81)}$ = 3.80, p = 0.051, η_p^2 = 0.183). We found an interaction between FP_{n-1} and FP_n ($F_{(4,68)}$ = 7.17, p < 0.001, η_p^2 = 0.297), as predicted by the previously reported asymmetry in sequential effects (Los et al., 2001). FP_{n-1} had a significant effect on mean RTs for short FP_n ($F_{(2,34)}$ = 11.32, p < 0.001 , η_p^2 = 0.400) and intermediate FP_n ($F_{(2,34)}$ = 12.27, P < 0.001, η_p^2 = 0.419). By contrast, there was no effect of FP_{n-1} on long FP_n ($F_{(1.08,18.43)}$ = 0.25, p = 0.643, η_p^2 = 0.014).

For short FP_n, responses were quickest when preceded by a short FP_{n-1} (313.24 ms, SE = 12.35). RTs increased by 24.1ms on average when the short FP_n was preceded by an intermediate FP_{n-1} (337.3 ms, SE = 15.25; $t_{(17)}$ = -3.30, p = 0.004) and by 49.7ms when the short FP_n was preceded by a long FP_{n-1} (362.9 ms, SE = 11.51; $t_{(17)}$ = -4.07, p = 0.001). For intermediate FP_n, responses were fastest when the intermediate FP_n was preceded by a short FP_{n-1} (284.2 ms, SE = 11.12).

RTs increased by 8.76ms on average when the intermediate FP_n was preceded by an intermediate FP_{n-1} (293ms, SE = 11.79; $t_{(17)} = -2.64$, p = 0.034) and by 20.6ms when it was preceded by a long FP_{n-1} (304.8 ms, SE = 11.51; $t_{(17)} = -4.50$, p < 0.001).

The asymmetry in sequential effects, that is, the interaction between FP_n and FP_{n-1}, was not modulated by ETU ($F_{(4,68)} = 0.37$, p = 0.832, $\eta_p^2 = 0.021$), ITU ($F_{(4,68)} = 1.86$, p = 0.128, $\eta_p^2 = 0.099$) or ETU and ITU combined ($F_{(4,68)} = 1.41$, p = 0.241, $\eta_p^2 = 0.076$). But the effects of FP_n ($F_{(1.16,19.70)} = 12.63$, p = 0.001, $\eta_p^2 = 0.426$) and FP_{n-1} ($F_{(2,34)} = 5.12$, p = 0.011, $\eta_p^2 = 0.231$) taken separately were both modulated by ETU.

Under conditions of low ETU, there was a marginally significant effect of FP_n on mean RT ($F_{(1.47,24.99)} = 2.82$, p = 0.092, $\eta_p^2 = 0.142$) driven by a significant 8.62ms reduction in RTs ($t_{(17)} = 3.26$, p = 0.01) for intermediate FP_n (280.3ms, SE = 14.14) compared to short FP_n (288.9ms, SE = 14.08). Under conditions of high ETU, FP_n had a similar but now significant effect on mean RTs ($F_{(2,34)} = 66.60$, p < 0.001, $\eta_p^2 = 0.797$) driven by a significant 35.6ms decrease in mean RTs for intermediate (296.2ms, SE = 10.95) compared to short FP_n (331.6ms, SE = 12.48; $t_{(17)} = 10.39$, p < 0.001) while there was no difference between intermediate and long FP_n (292.5ms, SE 11.84, $t_{(17)} = 0.913$, p = 0.374).

Under conditions of low ETU, FP_{n-1} had no effect on mean RTs ($F_{(2,34)} = 0.30$, p = 0.744, $\eta_p^2 = 0.017$). By contrast, for high levels of ETU, FP_{n-1} had a significant effect on mean RTs ($F_{(2,34)} = 21.14$, p < 0.001, $\eta_p^2 = 0.554$) driven by a 11.2ms increase in RTs for intermediate (307.1ms, SE = 10.87) compared to short FP_{n-1} (295.9ms, SE = 10.87; $t_{(17)} = -4.59$, p < 0.001) and a 10.6ms increase in RTs for long (317.7ms, SE = 12.54) compared to intermediate FP_{n-1} ($t_{(17)} = -2.76$, p = 0.026; see Figure 2.4).

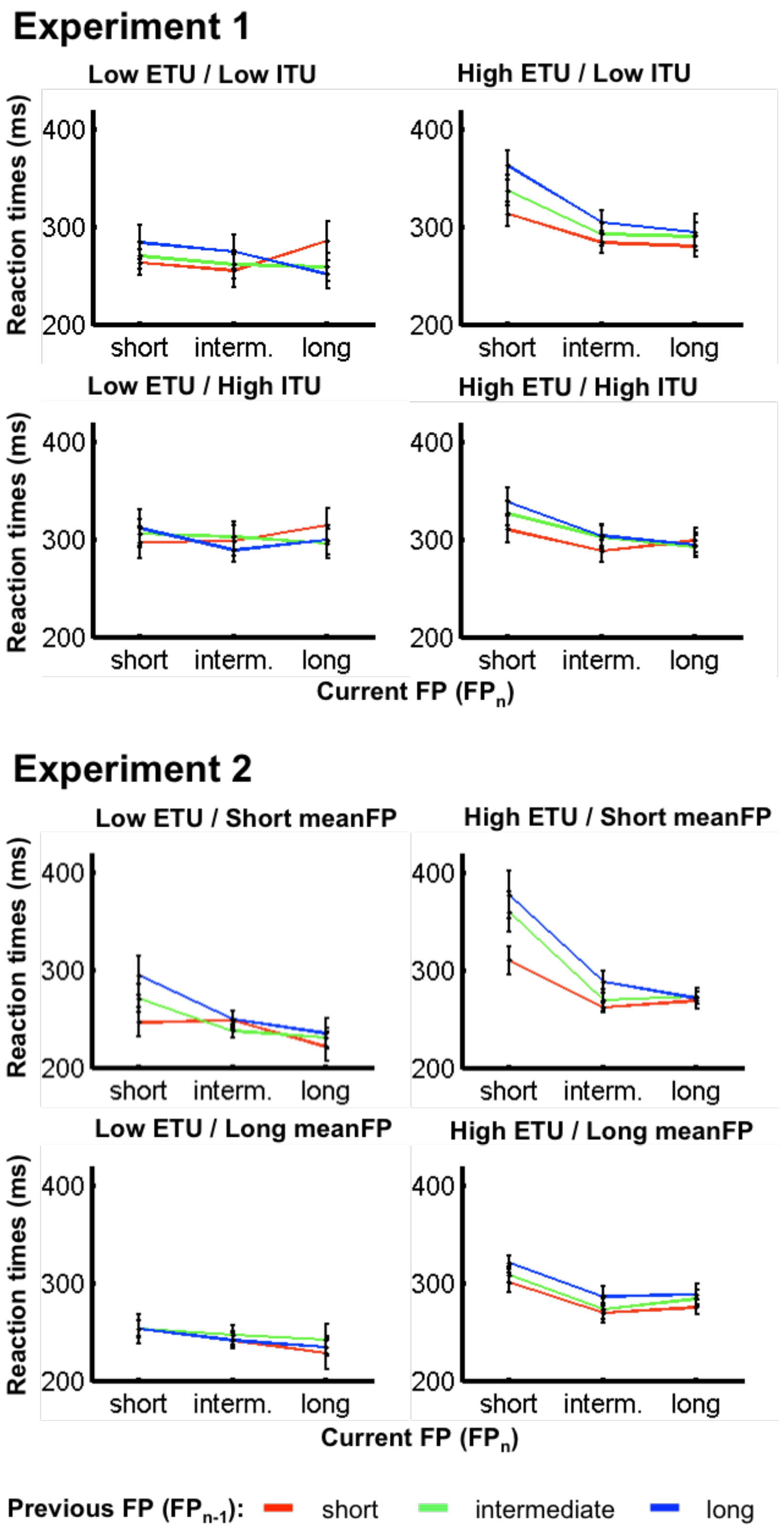


Figure 2.4: Sequential effects. Relation between reaction times (RTs) on the current trial and the foreperiod duration of the preceding trial for all four experimental conditions. *Experiment 1*: ETU and ITU. Preceding foreperiod duration has an effect on reaction times only for high levels of ETU. In addition, the difference in reaction time for intermediate compared to short *current* FP duration is attenuated for low levels of ETU. *Experiment 2*: ETU & meanFP. Effects of ETU on sequential effects (effect of preceding FP duration) disappear. Instead, meanFP interacts with the asymmetry in sequential effects (the relation between current and preceding foreperiod duration). The asymmetry in sequential effects disappears for long meanFP and, in addition, the effects of the preceding FP duration taken separately are attenuated. Experment 3: meanFP and FPvar. No significant effects. Errorbars show standard error.

Experiment 2: action preparation under conditions of ETU, when ITU is removed

The ANOVA for repeated measures revealed faster responses for low compared to high ETU ($F_{(1,14)}$ = 59.69, $p < 0.001$, η_p^2 = 0.810). By contrast, we found no significant main effect of meanFP ($F_{(1,14)}$ = 0.86, p = 0.370, η_p^2 = 0.58) and no significant interaction effect between meanFP and ETU ($F_{(1,14)}$ = 0.04, p = 0.849, η_p^2 = 0.003; see Figure 2.4).

The current FP (FP_n: $F_{(2,28)}$ = 24.24, $p < 0.001$, η_p^2 = 0.634) and the preceding FP (FP_{n-1}: $F_{(1.97,27.61)}$ = 10.10, p = 0.001, η_p^2 = 0.419) both affected mean RTs. The effect of FP_{n-1} was modulated by the effect of FP_n ($F_{(4,56)}$ = 6.14, $p < 0.001$, η_p^2 = 0.305), in line with the previously reported asymmetry in sequential effects (Los et al., 2001).

ETU did not modulate the effect of FP_{n-1} on mean RTs ($F_{(2,28)}$ = 1.40, p 0.264, η_p^2 = 0.091) or the asymmetry in sequential effects, that is, the interaction effect between FP_n and FP_{n-1} ($F_{(1,72,24.06)}$ = 1.18, p = 0.318, η_p^2 = 0.078). The effect of FP_n by contrast was modulated by ETU ($F_{(2,28)}$ = 12.35, $p < 0.001$, η_p^2 = 0.469): FP_n had a significant effect on mean RTs both under conditions of low ETU ($F_{(2,28)}$ = 11.84, $p < 0.001$, η_p^2 = 0.458) and high ETU ($F_{(1.42,19.84)}$ = 40.60, $p < 0.001$ η_p^2 = 0.744). Under conditions of low ETU, RTs progressively decreased for intermediate (244.4ms, SE = 6.62) compared to short FP_n (262.1ms, SE = 11.66; $t_{(14)}$ = 3.01, p = 0.018) and for long (232.27ms, SE = 9.12) compared to intermediated FP_n ($t_{(14)}$ = 2.68, p = 0.036). At high ETU, RTs decreased for intermediate FP_n (274.8ms, SE = 8.56) compared to short FP_n (329.6ms, SE = 11.68; $t_{(14)}$ = 9.00, $p < 0.001$) but not for long FP_n (277.4ms, SE = 7.07) compared to intermediate FP_n ($t_{(14)}$ = -0.49, p = 0.635).

In addition, meanFP interacted with FP_n ($F_{(1,44,16.02)} = 7.33$, $p = 0.013$, $\eta_p^2 = 0.344$) and with the asymmetry in the sequential effects, that is, the interaction between FP_n and FP_{n-1} ($F_{(1.86,26.07)} = 4.96$, $p = 0.017$, $\eta_p^2 = 0.262$).

A separate repeated measures ANOVA for short meanFP only, revealed significant main effects of both FP_n and FP_{n-1}($F_{(1.05,14.69)} = 12.14$,$p = 0.003$, $\eta_p^2 = 0.464$), $FP_{n-1\ (2,28)} = 4.60$, $p = 0.019$, $\eta_p^2 = 0.247$) and a significant interaction between FP_n and FP_{n-1} ($F_{(1.45,20.34)} = 4.61$, $p = 0.032$, $\eta_p^2 = 0.248$). Mean RTs were modulated by FP_{n-1} for short FP_n ($F_{(1.30,18.19)} = 12.82$, $p = 0.001$, $\eta_p^2 = 0.478$) and intermediate FP_n ($F_{(2,28)} = 4.12$, $p = 0.027$, $\eta_p^2 = 0.227$) but not long FP_n ($F_{(1.27,17.76)} = 0.91$, $p = 0.378$, $\eta_p^2 = 0.061$). Responses were fastest when the short FP_n was preceded by a short FP_{n-1} (278.4ms, SE = 13.41). When preceded by an intermediate FP_{n-1}, RTs increased by 37.18ms (315.6ms, SE = 16.70; $t_{(14)} = -4.60$, $p < 0.001$). When preceded by a long FP_{n-1}, RTs increased by 57.51ms (335.9, SE = 21.23; $t_{(14)} = -3.81$, $p = 0.004$). For intermediate FP_n, there was a trend towards faster responses if preceded by short FP_{n-1} (255.2ms, SE = 5.93) compared to long FP_{n-1} (269.1ms, SE = 9.13; $t_{(14)} = -2.00$, $p = 0.066$). There was no difference between effect of short and intermediate FP_{n-1} (253.8ms, SE = 8.41; $t_{(14)} = 0.24$, $p = 0.818$) on intermediate FP_n.

A separate repeated-measures ANOVA for long meanFP only, revealed significant effects of FP_n on RTs ($F_{(2,28)} = 16.95$, $p < 0.001$, $\eta_p^2 = 0.548$). The effect of FP_{n-1} was marginally significant ($F_{(1.43,20.07)} = 3.83$, $p = 0.051$, $\eta_p^2 = 0.215$) while the interaction between FP_{n-1} and FP_n was not significant ($F_{(2.72,38.08)} = 0.29$, $p = 0.881$, $\eta_p^2 = 0.021$). The significant effect of FP_n was driven by a significant 21.9ms reduction for intermediate FP_n (259.9ms, SE = 8.35) compared to short FP_n (281.7ms, SE = 7.41; $t_{(14)} = 6.70$, $p < 0.001$). There was no difference between intermediate and long FP_n (259ms, SE = 9.03; $t_{(14)} = 0.210$, $p = 0.837$). The marginally significant effect of FP_{n-1}

was driven by a significant increase of 6.4ms for intermediate (268.1ms, SE = 8.78) compared to short FP_{n-1} (261.5ms, SE = 8.88; $t_{(14)} = -2.06$; $p = 0.016$). There was no difference between intermediate and long FP_{n-1} (270.9ms, SE = 6.53; $t_{(14)} = -0.68$, $p = 0.51$).

Experiment 3: action preparation in the absence of ETU and ITU

A repeated-measures ANOVA revealed no significant effects of FPvar, meanFP, current FP (FP_n), and preceding FP duration (FP_{n-1}).

Taken together, explicit information about the timing of the IS removes sequential effects and with it any effects of varying foreperiod and mean foreperiod duration on those sequential effects (Experiment 3). Removing ITU, however, by providing an explicit and accurate external clock, does not remove the effects of meanFP on sequential effects (Experiment 2). Under conditions of both ETU and ITU (Experiment 1), ETU modulates the effect of current and, importantly, preceding FP duration on reaction times. But when ITU is removed (Experiment 2), this effect of ETU disappears. Instead, meanFP modulates the effects of FP_{n-1} on RTs and the asymmetry in sequential effect (the interaction between FP_n and FP_{n-1}).

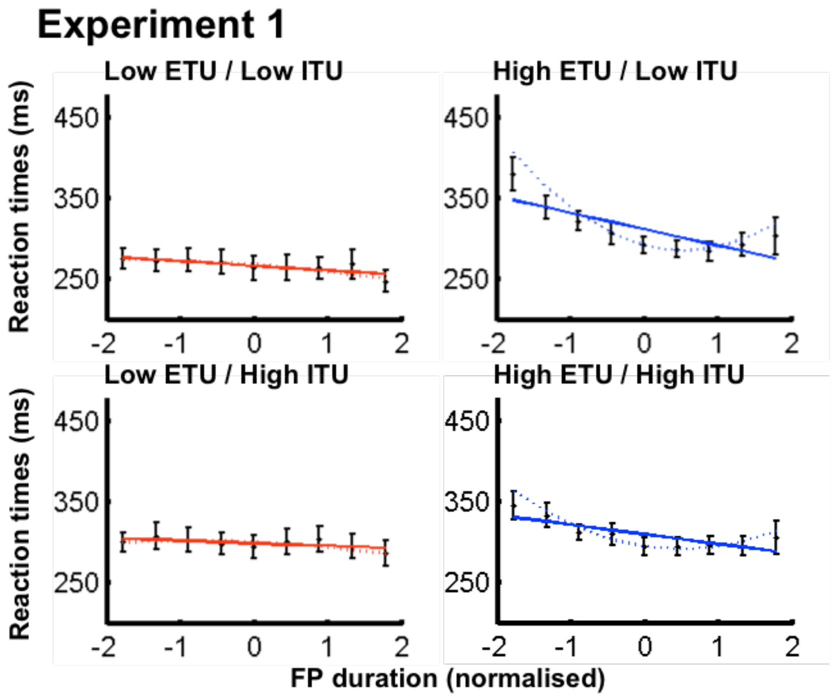
Foreperiod affect

Experiment 1: action preparation under conditions of ITU and ETU

Linear regression analyses revealed a weak to moderate relation between FP duration and RTs (Table 2.1). Inspection of residuals showed that the linear regression model systematically underestimated short and long FPs while it overestimated intermediate values (see Figure 2.5). Quadratic regression models were fitted to the RT data against standardised FP duration to explore whether these could provide a better fit. Unsigned residuals provide a measure of fit and a significant reduction in unsigned residuals for one versus another regression model (linear versus quadratic) would suggest a better fit. Paired t-tests on unsigned residuals, averaged across standardised FP duration, were used to test for a significant reduction, separately for each experimental condition. Only one of these four t-tests was significant after correction for multiple comparisons: the quadratic model provided a better fit of the RT data plotted against FP duration for low ETU at low ITU only ($t_{(17)} = 3.28$, $p = 0.018$). Given these results, the simpler regression model with fewer parameters was preferred and analysed further.

The ANOVA on the linear regression coefficients revealed that the change in RTs with increasing FP duration was pronounced for high versus low ETU *($F_{(1,17)} = 44.46$, $p < 0.001$, $\eta_p^2 = 0.723$),* but attenuated for high versus low ITU (*$F_{(1,17)} = 6.54$, $p = 0.020$, $\eta_p^2 = 0.278$*; see Figure 4). The interaction between ETU and ITU was marginally significant ($F_{(1,17)} = 3.18$, $p = 0.093$, $\eta_p^2 = 0.157$). This interaction was driven by a significant decrease in regression coefficients (i.e. a flattened slope) for high compared to low ITU at high ETU ($t_{(17)} = 2.68$, $p = 0.032$). At low ETU there was no difference between low and high ITU ($t_{(17)} = -1.17$, $p = 0.516$).

Finally, all regression coefficients were negative, revealing the predicted decrease in RTs with increasing FP duration. They were *significantly* different from zero in three out of the four experimental conditions, namely for low ETU / low ITU *($t_{(17)} = -4.04$, $p < 0.001$),* high ETU / low ITU *($t_{(17)} = -9.39$, $p < 0.001$)*, and high ETU / high ITU *($t_{(17)} = -4.56$, $p = 0.001$)*.



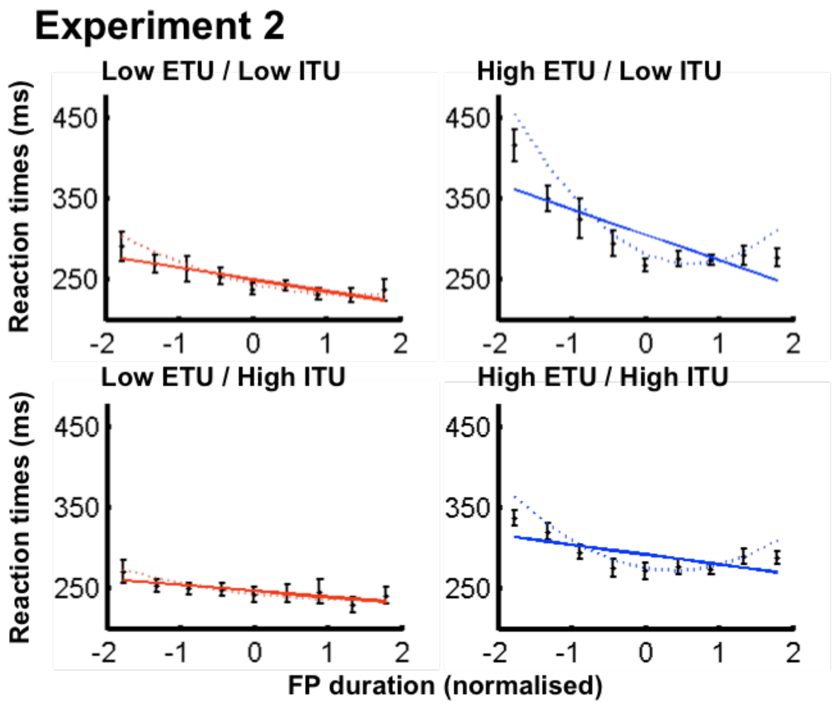


Figure 2.5: The foreperiod effect. Observed reaction time data (black diamonds) and the linear (solid line) and quadratic fits (dotted line) to the data for the four combinations of ETU and ITU (meanFP) in Experiment 1 and 2. *Experiment 1*: ETU and ITU and *Experiment 2*: ETU and meanFP. Reaction times decrease with increasing FP duration, but critically interact with the degree of ETU and ITU (meanFP) both in Experiment 1 and 2. For low levels of ETU, we found no difference in foreperiod effect between high and low levels of ITU. For high levels of ETU, we found an attenuated foreperiod effect under conditions of high ITU. Errorbars reflect the standard error.

Experiment 2: action preparation under conditions of ETU, when ITU is removed

Linear regression analyses revealed a moderate relation between FP duration and RTs (Table 2.1). As before, the inspection of residuals showed that the linear regression models systematically underestimated short and long FPs and overestimated intermediate values (see Figure 2.5). Quadratic regression models were fitted to the RT data against standardised FP duration to explore whether these could provide a better fit. Paired t-tests on unsigned residuals, averaged across standardised FP duration, were used to test for a significant reduction in residuals, separately for each experimental condition. Only one of these t-tests turned out to border on significance after correction for multiple comparisons: for high ETU and long meanFP ($t_{(14)} = 2.86$, $p = 0.050$). Given these results, the simpler linear model was preferred and linear regression coefficients were analysed further.

A repeated-measures ANOVA on linear regression coefficients revealed a significant main effect of meanFP($F_{(1,14)} = 11.25$, $p = 0.005$, $\eta_p^2 = 0.446$) and ETU ($F_{(1,14)} = 29.49$, $p < 0.001$, $\eta_p^2 = 0.677$). Also, the interaction between ETU and meanFP was significant ($F_{(1,14)} = 8.50$, $p = 0.011$, $\eta_p^2 = 0.378$). This interaction was driven by a slower decrease in RTs with FP duration, a flattened slope, for long compared to short meanFP under conditions of high ETU ($t_{(14)} = -3.63$, $p = 0.006$). At low ETU, there was no difference between short and long mean FP duration ($t_{(14)} = -2.12$, $p = 0.16$; see Figure 2.5).

Finally, all regression coefficients were negative and differed from zero in all experimental conditions (low ETU/ short meanFP: $t_{(14)} = -3.67$, $p = 0.002$; high ETU/ short meanFP: $t_{(14)} = -7.02$, $p < 0.001$; low ETU/ long meanFP: $t_{(14)} = -3.73$, $p < 0.001$; high ETU / long meanFP: $t_{(14)} = -8.21$, $p < 0.001$).

Experiment 3: action preparation in the absence of ETU and ITU

The linear regression models explained a weak to moderate amount of variance in the RT data (Table 1). There was no clear systematic pattern in residuals, unlike in the previous analyses of the FP effect. Therefore, the regression coefficients of the linear models were analysed further. The ANOVA on regression coefficients revealed no significant effects. Also, none of the regression coefficients differed from zero.

In summary, explicit information about IS timing removes any effect of mean FP and FP variability (Experiment 3) on the FP effect. By contrast, removal of ITU by means of an accurate external time-keeper (Experiment 2) did not remove the effects of meanFP. Instead, the effects of ETU and ITU (Experiment 1) or meanFP (Experiment 2) on the FP effect were similar regardless of the presence of absence of an accurate external time-keeper. The FP effect increases for high levels of ETU but only if ITU (meanFP) is sufficiently low (short). Effects of ETU and ITU on the FP effect may not be dissociable – they can only be removed together or not at all.

Discussion

In a series of three experiments, we examined the effects of internal (ITU) and external temporal uncertainty (ETU) on temporal preparation using a modified variable foreperiod (FP) simple reaction time task. Both types of temporal uncertainty are likely to influence action preparation, but their origin is fundamentally different. ETU originates in the environment and arises when the timing of imperative varies from one instance to the next. ITU arises from inaccurate internal clocks. To prepare for impending actions in the face of ETU and ITU, both quantities need to be estimated, represented and temporal preparation needs to be adjusted accordingly.

The main results reported here show that ETU and ITU interact in the way they affect behaviour, and have distinct influences on how fast participants respond to imperative events. While some effects of ITU cannot be fully dissociated from effects of ETU, participants *can* control for temporal uncertainty under conditions in which reliable information about the time of occurrence of imperative events is provided. As such, the current study strongly supports strategic accounts of temporal preparation (Drazin, 1961; Nobre et al., 2007; Requin & Granjon, 1969) as opposed to the automatic account (Los & van den Heuvel, 2001; Los & Heslenfeld, 2005; Los et al., 2001), and sheds novel light onto the processes underlying the preparation of action in a (temporally) uncertain world.

Experiment 1: summary of results

Experiment 1 was conducted to investigate the effects of ETU, ITU, and their possible interaction on temporal preparation. Overall, participants responded faster under conditions of low ITU. Moreover, ETU and ITU interacted in their effects on participants' consistency in the time it took them to respond to the IS: participants were more variable when ETU was high but only under conditions of low ITU.

Second, we asked whether and how ETU and ITU affect sequential effects. In line with previous work (S A Los & van den Heuvel, 2001; S. Los & Heslenfeld, 2005; S. Los et al., 2001) reaction times revealed both strong sequential effects and an asymmetry in those sequential effects. For short FP_n, compared to intermediate or long FP_n, long FP_{n-1}, for example, had the strongest effect on RTs in that long FP_{n-1} lead to a comparatively strong increase in RT on the current trial. This asymmetry in sequential effects was not modulated by ETU or ITU. The sequential effect itself, however, was modulated by the degree of ETU, being present only under conditions of high levels of ETU.

Third, we asked whether ETU and ITU modulate the FP effect (Drazin, 1961; Los et al., 2001; Nobre, Correa, & Coull, 2007; Requin & Granjon, 1969; Vallesi, Shallice, & Walsh, 2007). We found that high ETU increases the FP effect, whereas the FP effect is attenuated under conditions of high ITU. In addition, there is a further reduction in the FP effect for high levels of both ETU and ITU. The FP effect disappears entirely when ETU is low and ITU is high.

Experiment 2: summary of results

In Experiment 2, we removed ITU to study the influence of ETU on preparation for action in isolation. Introducing an accurate, external clock to remove ITU, differences in RTs were now driven entirely by ETU. On average, high ETU delayed participants' responses. Similarly, high ETU increased participants' variability in RTs.

While ETU did not modulate sequential effects we found that the mean FP duration (i.e. ITU in Experiment 1) interacted with the asymmetry in sequential effects. While we found both sequential effects and an asymmetry in sequential effects for short mean FP duration, we found a mere trend towards sequential effects and no asymmetry for long mean FP duration. This pattern of findings is puzzling. We had two competing predictions for Experiment 2: the effects of ITU disappear, or are comparable to the effects observed when being exposed to both ETU and ITU. We return to this issue in the general discussion.

We observed a stronger FP effect under conditions of high ETU regardless of mean FP duration. But if on average long FPs preceded the imperative event (long meanFP), then the FP effect is generally weaker. Removing ITU by means of an accurate external clock did thus not remove effects of mean FP duration on the FP effect. The FP effect was now present, however, in all four experimental conditions, unlike in Experiment 1.

Experiment 3: summary of results

In Experiment 3 we asked whether the effects of ETU and ITU can be removed altogether by providing explicit and reliable information about both the passage of time and the time of occurrence of the IS. The removal of both types of temporal uncertainty abolished any behavioural differences driven by mean FP duration (ITU in Experiment 1) or its variability (ETU in Experiment 1 and 2). Moreover, providing explicit and reliable information abolished both the FP effect and sequential effects.

The results reported here clearly show that ETU and ITU affect behaviour and have distinct influences on how quickly and consistently participants can respond to imperative events. While some effects of ITU may not be fully dissociable from effects of ETU, participants *can* control for temporal uncertainty under conditions in which reliable information about the time of occurrence of imperative events is provided. As such, the current study supports strategic accounts of temporal preparation as opposed to the automatic account.

Effects of temporal uncertainty on reaction times and their variability

When exposed to both ETU and ITU (Experiment 1), responses to imperative events are faster when levels of internal temporal noise are low (i.e. ITU). Responses are also less variable when imperative events are more predictable in time, but this effect is prominent only when internal uncertainty is also low. When participants experience high levels of internal uncertainty, then the (un)predictability of an event has relatively little additional impact on variability in preparation. When removing ITU

(Experiment 2), temporal preparation improves and becomes less variable if an imperative event is temporally predictable. This result appeals to intuition: the less variable events are in time, the better we can prepare for them. Importantly, the effects of ITU can be removed when explicit information about the passage of time is provided, which suggests that the effects of ETU and ITU are dissociable. Furthermore, comparison of Experiment 1 and 2 shows that ETU and ITU interact rather than being merely additive: in the face of high ITU one cannot benefit from stimulus occurrence being predictable in time, i.e. having low ETU (Experiment 1). However, when ITU is removed, and participants are aware of the passage of time, participants respond faster to predictable imperative events regardless of preceding mean FP duration (Experiment 2). Finally, when accurate information about the timing of imperative events is also provided (Experiment 3), then neither their variability in time (ETU in Experiment 1) nor the average duration of the FP preceding these imperative events (ITU in Experiment 1), affects reaction times or variability in reaction times. Thus, given appropriate temporal information, participants can overcome both the temporal uncertainty inherent in imperative events and their noisy internal clocks.

Our results thus show that endogenous cues, such as warning cues that provide temporal anchor points, are used for temporal preparation. The quality with which such a reference can be used for temporal preparation decreases with increasing variability of imperative events (ETU) and with increasing internal temporal noise (ITU). Preparation is therefore less likely to be aligned with an imperative event when its temporal predictability is low, and when internal temporal noise is high.

Finally, when ITU is removed (Experiment 2), then effects of the average time interval preceding the imperative event disappear. These results provide strong evidence in favour of strategic accounts of temporal preparation (Alegria & Delhaye-

Rembaux, 1975; P Bertelson, 1967; Drazin, 1961; Klemmer, 1956, 1957; J Requin, 1969; Vallesi, Mussoni, et al., 2007; Vallesi et al., 2009; Vallesi & Shallice, 2007; Vallesi, Shallice, et al., 2007) in which explicit information can be used to adjust preparation in the face of events variable in time. These conclusions are further bolstered by our final experiment, in which both ETU and ITU were both removed. This effectively abolished any behavioural effects caused by FP variability or mean FP duration. The effects of ETU and ITU can in fact be overcome through explicit guidance that removes the requirement to estimate temporal uncertainty for the preparation of action.

Of note is that some previous studies have also aimed at reducing the effects of temporal uncertainty by providing participants with informative cues about the FP duration on a trial (S A Los & van den Heuvel, 2001; S. Los & Heslenfeld, 2005; S. Los & Schut, 2008; Steinborn et al., 2008). Such manipulations remove uncertainty about when the imperative stimulus will appear (ETU), but still require participants to track the passage of time, and therefore do not remove internal temporal uncertainty. Providing foreknowledge about either ITU or ETU is therefore distinct from actually removing it, and does not allow for isolating the processes assigned to estimate, represent, and implement appropriate changes in behaviour in the face of ETU, ITU, or both.

The role of temporal uncertainty on sequential effects

Our analyses of sequential effects confirm that the duration of the FP of a preceding trial impacts on action preparation on the next trial. In other words, participants use the most recent information about FP duration for future action preparation. As such, they use the available exogenous cues for temporal preparation, even though these may be misleading: in the present case there was no causal relationship between subsequent FPs. Importantly, when exposed to both

ETU and ITU (Experiment 1), sequential effects are significantly influenced by the level of ETU, being stronger for high ETU. This finding may be due to bigger differences in FP duration between two consecutive FPs when ETU is generally high. In other words, when ETU is low, the difference between two consecutive FPs is likely to be small whereas, when ETU is high, this difference is likely to be relatively large. These larger differences in FP duration may lead to bigger differences in reaction times and thus stronger sequential effects.

This explanation implies, however, that sequential effects do not ‘scale’ with ETU. The effect of a preceding trial’s FP duration on preparation for future imperative events is fixed and determined by the *absolute* difference in FP duration between two consecutive trials. It does not scale (i.e. change proportionally to the overall ETU of a particular environment). That is, even if an environment is relatively unpredictable, the most recent information available is used to the same extent as when an environment is relatively stable. Interestingly, the effect of ETU on sequential effects disappears when ITU is removed. This suggests that when reliable information about the passage of time is available sequential effects do scale with the overall ETU depending on how well one can track the passage of time.

An alternative explanation we propose here is that the effects of ETU on sequential effects may be driven, at least in part, by the level of ITU. In constant FP tasks participants might use the preceding FP duration for improving their time interval estimation by ‘recalibrating’ their internal clock based on the timing of the preceding imperative event. This may be required if the IS is perceived as occurring earlier or later than expected, which will be the case when an internal clock is inaccurate. When imperative events vary in time, participants may still attempt to use the timing of imperative events to recalibrate clock speed. In other words, if an imperative event occurs later than expected participants may adapt the speed of their internal clock such that it matches again with their temporal prediction of when the event was most likely to occur. This would also lead to being unprepared when a subsequent imperative events occurs earlier than expected, which is the signature of sequential effects. Albeit speculative, this proposal can explain why the level of ETU does not affect sequential effects when information about the passage of time is provided: in such cases there is no requirement to recalibrate internal clocks.

Finally, when explicit and reliable information about the timing of the imperative event was provided (Experiment 3), then sequential effects disappeared. This further supports the strategic account of temporal preparation and is evidence against the conditioning account. To our surprise, however, we found that when ITU was removed by an accurate external clock, mean FP duration (ITU in Experiment 1) remained affecting sequential effects. This finding suggests that effects of ITU cannot be removed selectively. Only full removal of temporal uncertainty, both ETU and ITU, abolishes effects of temporal uncertainty. In other words, participants cannot dissociate the effects of ETU and ITU on sequential effects. Only when they are not required to track time at all, when information about timing of the IS is given, do effects of temporal uncertainty disappear.

The role of temporal uncertainty on the FP effect

As in previous work (P Bertelson, 1967; P Bertelson & Tisseyre, 1968; Jean Requin & Granjon, 1969; Vallesi & Shallice, 2007), our results reveal a linear relation between FP duration and reaction times. Overall, reaction times tend to decrease with increasing FP duration, which is the hallmark feature of the FP effect. One key observation is that when exposed to both ETU and ITU (Experiment 1), the FP effect depends on the specific level of ETU and ITU, respectively. The FP effect is stronger when imperative events are unpredictable but reduced when internal temporal uncertainty is high. Furthermore, it disappears completely for combination of low levels of ETU and high levels of ITU. When ITU was removed (Experiment 2), we found a comparable modulation of the FP effect by ETU and mean FP duration, but in contrast to Experiment 1 there was now a progressive decrease in reaction times with increasing FP duration for all experimental conditions. Finally, when accurate information about the timing of the imperative events was provided (Experiment 3), FP effects disappear altogether.

Collectively our results can be taken as indication that the passage of time is in itself a cue for action preparation when participants experience either ETU alone (Experiment 2), or in conjunction with ITU (Experiment 1). However, to which extent the passage of time can be used depends on the specific levels of ETU and ITU. Critically, accurate estimates of time are necessary for computing the conditional probability of imperative events (i.e. the hazard rate), a process that is presumed to underlie the FP effect (Nobre et al., 2007). With increasing internal temporal noise (high ITU), estimates of the hazard rate may become too inaccurate and inefficient for temporal preparation. Importantly, this implies that the FP effect may disappear because of noisy internal clocks and not because of an inability to track changes in conditional probability *per se*. One may erroneously conclude, based on weak FP effects, that participants were not keeping track of conditional probabilities of imperative events when, in fact, high levels of intrinsic temporal noise could have influenced their temporal preparation.

By contrast, the FP effect is stronger when ETU is high. There are two competing explanations for this finding. At high ETU levels, the rate of change in the conditional probability of imperative events is relatively small (see Figure 2.1B), which may facilitate the tracking of these changes. Alternatively, the subjective estimate about the conditional probability might be the same for both conditions of ETU, but participants may find it more difficult to translate this estimate into adequate levels of preparation when ETU is low as they would have to implement corresponding changes in preparation more quickly at a higher rate.

Removing ITU does not eliminate the effect of the average FP preceding the imperative event (ITU in Experiment 1) on the FP effect (i.e. the decrease in reaction times with increasing FP duration). Removing ITU may lower the intercept of the linear relation between FP duration and reaction times (i.e. responses are overall faster, which explains why mean FP duration does not affect mean reaction times in Experiment 2, see Figure 2.3). However, the regression coefficient, which indexes the strength of the FP effect, is not affected by removing ITU. Only removal of all temporal uncertainty, both ETU and ITU, abolishes FP effects (Experiment 3). This result speaks against the FP effects being caused by automatic processes. Rather, the effect of ITU on the FP effect may not be dissociable from the effects of ETU: effects can only be removed together when keeping track of time becomes obsolete thanks to an accurate external “stop-watch” (cf. conclusions regarding dissociability of effects of ETU and ITU on sequential effects).

The importance of the distinction between ETU and ITU

The effects of ETU and ITU on the various signatures of temporal preparation highlight the importance of distinguishing between, or controlling for, these two types of temporal uncertainty. The present results strongly suggest that temporal preparation in variable FP tasks engages multiple processes that serve to estimate, represent, and implement appropriate changes in behaviour in the face of ETU and ITU. These processes can interact in any number of ways. For example, the present study suggests that a proportion of sequential effects may be due to participants' attempts to compensate for internal temporal uncertainty.

The putative interaction with event preparation

Distinguishing ETU and ITU is important for several reasons. For example, previous work has addressed how information about ‘what’ action to perform and ‘when’ to perform it might be combined for action preparation (P Bertelson & Barzeele, 1965; Sanders, 1990; Spijkers, 1990; Spijkers & Walter, 1985). Our results suggest that such investigations cannot reveal the specific process that binds together preparation for ‘what’ to do and ‘when’ to do it because of the inherent interaction between the different types of temporal uncertainty. Addressing this long-standing question therefore requires investigation of how internal and external temporal uncertainty, respectively, influence action preparation when alternative actions are viable (‘what’ preparation).

ETU and ITU in health and disease

Our findings are further relevant for work on impairments in timing behaviour in neuropsychiatric disorders (for a review, see (Allman & Meck, 2011). For example, previous work has revealed abnormal performance on *explicit timing* tasks in patients with Parkinson’s Disease (PD; (Artieda et al., 1992; Jones et al., 2008; Koch et al., 2008; Lange, Tucha, Steup, Gsell, & Naumann, 1995; Merchant, Luciana, Hooper, Majestic, & Tuite, 2007; Pastor et al., 1992). Similarly, performance on variable FP tasks differs from controls in patients with PD (JAHANSHAHI, BROWN, & MARSDEN, 1992; Jurkowski et al., 2005). Internal clocks therefore appear to be noisier following dopamine depletion (Jurkowski et al., 2005). This interpretation is congruent with the idea that intact dopamine in the basal ganglia is a crucial neurobiological pre-requisite for time perception (for reviews, see (Jennifer T Coull et al., 2011; Jones & Jahanshahi, 2009b).

Work on clinical populations, however, has not distinguished between ETU and ITU, therefore precluding more specific interpretations about the origins of the observed deficits in the variable FP task in these patients. The observed deficits of PD patients in variable FP tasks (JAHANSHAHI et al., 1992; Jurkowski et al., 2005) may be caused by deficits in extracting temporal structure from the environment, by an abnormally noisy internal clock, or both. In other words, either the estimation or representation of ETU and / or ITU, or the processes that implement behaviour in the face of ETU and ITU may be affected in PD patients. Further studies that distinguish between ETU and ITU may provide further insights into the origin of impaired explicit and implicit timing behaviour in this patient population.

Similarly, performance on implicit and explicit timing tasks is more variable in patients suffering from schizophrenia (Allman & Meck, 2011; Carroll, Boggs, O'Donnell, Shekhar, & Hetrick, 2008; Carroll, O'Donnell, Shekhar, & Hetrick, 2009; Smyrnis et al., 2009), suggesting abnormally inaccurate internal clocks in these patients. Furthermore, in implicit timing tasks, such as the FP task, schizophrenic patients show a 'cross-over effect': patients are faster on variable FP tasks compared to constant FP tasks if constant FP duration exceeds 3000ms (Borst & Cohen, 1987, 1989). Some have attributed this cross-over effect to higher levels of internal temporal noise in schizophrenic patients (Borst & Cohen, 1989). Providing explicit information about the passage of time reduced reaction times but did not abolish the cross-over effect (Borst & Cohen, 1989). Interestingly, the current study suggests that effects of ITU on the FP effect cannot entirely be dissociated from effects of ETU and removed selectively. Thus, a residual cross-over effect in schizophrenic patients, despite accurate information about the passage of time, is consistent with our data and suggests that internal temporal noise is indeed increased in these patients. In addition, however, schizophrenia patients may also suffer from impairments in extracting the temporal structure of events, which may be masked by high internal temporal noise (ITU). In other words, patients may not be able to discover regularities in the timing of imperative events because their internal clocks are too noisy to reliably detect such regularities. Future studies that distinguish between ETU and ITU, in the way introduced in this series of experiments, will be able to determine the origins of abnormal performance on variable FP paradigms in PD, schizophrenia, and other disorders characterised by impairments in time estimation.

Conclusions

Being prepared for action is a paramount requirement in an uncertain world. In a series of three experiments, we studied the impact of ETU and ITU, two types of temporal uncertainty, on temporal preparation. We found differential effects of ETU and ITU on the overall level and consistency of temporal preparation, sequential effects, and the FP effect. As such, we demonstrated that both the level of temporal uncertainty *and* its origin determine how temporal uncertainty is dealt with in preparing for imperative events in an uncertain world. Finally, we provide evidence for the strategic account on temporal preparation: effects of temporal uncertainty can be fully removed by explicit information about the timing of imperative events. However, different types of temporal uncertainty may not be fully dissociable: it may not be possible to remove one without the other. We conclude that two distinct processes may be concerned with the estimation of ETU and ITU and differentially affect preparation for action in an (temporally) uncertainty world.

Chapter 3: How the *origin* of temporal uncertainty affects event preparation

Abstract: Are there beneficial effects of knowing *what* action to prepare for when there is no information about *when* to act (*temporal uncertainty*)? Conversely, does information about action timing improve action preparation when there is no information about what action to prepare for (*event uncertainty*)? In two experiments, we explored the interplay between temporal and event uncertainty on action preparation. Temporal uncertainty was distinguished by origin. Temporal uncertainty is external when it is due to an unpredictable world (i.e. variability of imperative stimuli in time; ETU). Internal temporal uncertainty (ITU) arises as a consequence of noisy time perception. In Experiment 1, participants completed a variable foreperiod choice reaction time task. ETU was manipulated by foreperiod variability. ITU was removed by an accurate external time-keeper. Event uncertainty was manipulated by frequency imbalance of action alternatives. Results revealed that benefits of low external temporal uncertainty are apparent only when event uncertainty is low. In Experiment 2, participant completed a constant choice reaction time task. Prior to this, participants completed a time interval reproduction task (Bridging Experiment). Their standard deviation in reproduced target intervals provided a measure of their ITU. Foreperiods were then chosen, based on data of the Bridging Experiment, to match the level of temporal uncertainty across Experiments 1 and 2. Experiment 2 revealed that high ITU has detrimental effects on preparation only when event uncertainty is high. Taken together, these results show, for the first time, that effects of *knowing what* and *knowing when* depend on the *origin* of temporal uncertainty. When temporal uncertainty is external, then one has to know what to benefit from knowing when. When temporal uncertainty is internal, then high temporal uncertainty can be compensated for but only if there is information about what action to prepare for.

Key words: action preparation, choice reaction time task, temporal uncertainty, event uncertainty, implicit timing

For efficient preparation and quick execution of motor action, both knowing *what* to do and knowing *when* to do it is crucial. For example, when playing tennis, a perfect forehand volley is useless when its timing is off. Conversely, even if perfectly timed, a forehand volley is unlikely to win a point when a backhand volley would have been more appropriate. In this chapter, we address how advance information about *what* to do and about *when* to do it affects preparation and execution of motor action. We asked whether one can successfully prepare for motor action under conditions of limited knowledge about either *what* to do or *when* to do it.

Information about *what* action to prepare for may be a prerequisite for being able to use information about *when* to respond. Conversely, knowing *when* to act may be necessary to benefit from knowing *what* to do. Alternatively, information about *what* to do and *when* to do it may be used independently: one may benefit from knowing *what* or *when* even when the other piece of information is missing. This chapter presents two experiments that explore the relation between advance information about the type of forthcoming motor action (*what*; *event uncertainty*) and about its timing (*when*; *temporal uncertainty*). We distinguished between the external (ETU) and internal (ITU) origin of temporal uncertainty (Klemmer, 1956, 1957). We asked whether the origin of temporal uncertainty determines how we use advance information about the type of forthcoming motor action or action timing. In other words, does it matter for preparation for action whether temporal uncertainty originates from an unpredictable world or noisy time perception?

Action preparation typically benefits from low event uncertainty (Fitts, 1992; Fitts & Peterson, 1964; Hick, 1952; Hyman, 1953; Schneider & Anderson, 2011). Similarly, low temporal uncertainty improves preparation for action (Bertelson, 1967; Bertelson & Tisseyre, 1968; Carlsen & Mackinnon, 2010; Davis, 1962; Drazin, 1961; Hohle, 1965; Klemmer, 1956, 1957; Los & Schut, 2008; Zahn & Rosenthal, 1966; for reviews, see Hackley, 2009; Niemi & Naatanen, 1981). Event and temporal uncertainty are assumed to independently affect action preparation (Bertelson & Boons, 1960; Holender & Bertelson, 1975; Spijkers, 1990; Spijkers & Walter, 1985). It has been suggested that event preparation and temporal preparation are supported by two independent preparatory processes (Holender & Bertelson, 1975), which may take place at different discrete processing stages (Sanders, 1990; Spijkers, 1990; Spijkers & Walter, 1985). But problematically, all of these studies have looked at the effects of either ITU (Bertelson & Barzeele, 1965; Holender & Bertelson, 1975; Spijkers, 1990) or ETU and ITU combined (Bertelson & Boons, 1960; Sakai et al., 2000). The effects of ETU on preparation for action have not yet been studied in isolation, and have not yet been compared to the effects of ITU. Importantly, ETU and ITU may differ in their effects on behaviour. The relation between temporal and event uncertainty may be influenced by, or entirely depend on, the external (ETU) or internal (ITU) origin of temporal uncertainty. At the behavioural level, putative interaction effects between event and temporal uncertainty may cancel out when both ETU and ITU are experienced in conjunction (Bertelson & Boons, 1960; Sakai et al., 2000). For example, participants may benefit more from low ETU when event uncertainty is low, because they are then able to prepare the appropriate action at the appropriate time. By contrast, participants may be able to compensate for high ITU when they are not also simultaneously hampered by high event uncertainty. If this were the case and if ETU and ITU were then experienced together, putative interaction effects with event uncertainty would cancel out, at least partially. One would expect to observe a (comparatively smaller) difference in reaction times for high versus low temporal uncertainty under conditions of low event uncertainty, primarily driven by better preparation under conditions of low ETU. Similarly, one would expect to find a (comparatively smaller) reaction time difference for high versus low temporal uncertainty under conditions of high event uncertainty primarily driven by a lack of compensation for high ITU. This pattern in reaction times has been previously reported (Bertelson & Barzeele, 1965; Cotti et al., 2011; Holender & Bertelson, 1975; Sakai et al., 2000; Spijkers, 1990; Spijkers & Walter, 1985). We ask whether it can be explained by independent processes for event and temporal preparation, as previously suggested, or whether the origin of temporal uncertainty determines the interaction between temporal and event uncertainty.

As participants experience ITU whenever they are required to estimate time, either explicitly or implicitly, one needs to explicitly remove ITU in order to investigate the effects of ETU in isolation. This can be achieved experimentally by using accurate external time keepers (Borst & Cohen, 1989; Jean Requin & Granjon, 1969) such as, for example, stopwatches (Carlsen & Mackinnon, 2010). In two experiments, we here explored the relation between ETU, ITU, and event uncertainty. In Experiment 1, we asked how event uncertainty and ETU interact when ITU is removed. In Experiment 2, we asked whether the relation between event and temporal uncertainty depends on the external or internal origin of temporal uncertainty. To explore the effect of origin on the relation between event and temporal uncertainty, the level of ITU and ETU that participants experienced had to be comparable. In other words, participants had to experience the same *level* of temporal uncertainty, external or internal, in addition to event uncertainty to explore the effects of the *origin* of temporal uncertainty. We therefore estimated the level of ITU associated with time intervals of several durations to match Experiment 1 and 2 with regard to the level of temporal uncertainty whilst exploring the effects of its external or internal origin (see Figure 3.1).

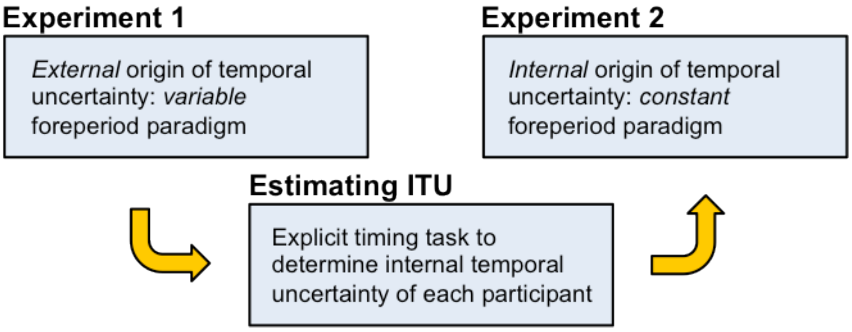


Figure 3.1: The interplay between *knowing what?* (event uncertainty) and *knowing when?* (temporal uncertainty) explored for an internal (ITU) and external (ETU) origin of temporal uncertainty. External temporal uncertainty (ETU) arises from an unpredictable world when the timing of imperative events varies from one instance to the next. Internal temporal uncertainty (ITU) arises as a consequence of noisy internal clocks. Experiment 1 investigated the relation between ETU and event uncertainty. Experiment 2 studied whether the relation between temporal and event uncertainty depends on the external or internal origin of temporal uncertainty. A bridging experiment was conducted to match Experiment 1 and 2 with regard to the level but not origin of temporal uncertainty that participants experienced. This allowed direct statistical comparison between Experiment 1 and 2 and could reveal the importance of the *origin* of temporal uncertainty (external or internal) for the relation between temporal and event uncertainty.

Experiment 1

In Experiment 1, we assessed the relation between ETU and event uncertainty, whilst removing ITU. We removed ITU by providing explicit information about the passage of time (Borst & Cohen, 1987; Jean Requin & Granjon, 1969). In addition, we asked how ETU and event uncertainty interact for two different hazard functions (Coull, Cheng, & Meck, 2011; Nobre, Correa, & Coull, 2007). A hazard function describes the probability of the imperative event occurring at any given time during the preparatory period (for example “now!”) given that it has not yet occurred (i.e. the posterior probability of the imperative event, or hazard rate). For a Gaussian distribution, for example, this hazard rate will increase monotonically over time. Participants may use their estimate about the hazard rate (i.e. the probability that the imperative event occurs “now!”) to prepare for action and, effectively, to reduce ETU (Coull et al., 2011; Nobre et al., 2007). In other words, this estimate that the imperative event has not yet occurred informs about the timing of the forthcoming imperative event. As such, it provides additional advance information about action timing, which accumulates throughout the foreperiod, and gradually reduces ETU.

In the present experiment, we used two hazard functions. In one condition, the posterior probability of the imperative event increased throughout the foreperiod. By contrast, in the other condition this probability increased, peaked, and then declined. The first hazard function can be thought of as an analogue of situations where imperative events are bound to occur, after a set interval with some temporal variation, for example, when waiting for a traffic light to change colour. The latter represents situations where imperative events may or may not occur after a given time (again with some temporal variation), such as when waiting for a date to show up (or, sadly, in some cases not). This manipulation allowed us to address whether any interaction between ETU and event uncertainty depended on the specific type of hazard function. We included this manipulation because only ETU, but not ITU, can be gradually reduced by the hazard function over time. Any interaction between event uncertainty or ETU and the type of hazard function would reveal a crucial difference between ETU, ITU, and their respective effects on behaviour. Further, including two hazard functions allowed us to dissociate the time course of preparation from the mere passage of time. If preparation follows the hazard rate (Nobre et al., 2007; Jean Requin & Granjon, 1969) then it develops gradually over time. Including two hazard functions allows dissociating preparation from the mere passage of time, as participants' preparation should develop gradually over time *depending* on the hazard functions. If two hazard functions are different, then preparation over time should differ.

Given previous findings, one may expect to find independent additive effects of ETU and event uncertainty on reaction times (Bertelson & Boons, 1960; Cotti et al., 2011; Sakai et al., 2000). In this case, action preparation should benefit from low levels of ETU irrespective of the level of event uncertainty, and vice versa. By contrast, ETU may interact with event uncertainty. For example, participants may benefit more from low ETU when they know which action to prepare for because, in this case, they will be able to prepare the appropriate action at the appropriate time. Finally, we held no specific predictions about how the type of hazard function might interact with the predicted relationship between event uncertainty and ETU. We speculated that the nature of preparation, in particular how ETU is processed, does not depend on how the probability of the imperative event develops throughout the foreperiod. In this case, the type of hazard function should not interact with event uncertainty, ETU, or their possible interaction.

Methods

Participants

12 participants (mean age = 20.4 years, age range = 19 – 24 years, 3 males, 3 left-handed) with normal or corrected-to-normal vision took part in this study. They were reimbursed for time and travel (£20). Before the experiment, participants gave written informed consent. This study was conducted with the approval of a local ethics committee and in line with the declaration of Helsinki.

Apparatus

The experiment was run on a desktop computer, using the cogent 2000 toolbox (http://www.vislab.ucl.ac.uk/cogent.php) running under Matlab 7.5 (Mathworks, Natick, MA). Stimuli were presented on a 19’ LCD screen with a refresh rate of 60Hz. Participants responded by pressing right < AltGr > and < Ctrl > keys with their right index and little finger, respectively, on a standard QWERTY keyboard.

Experimental procedure

Participants performed a modified variable foreperiod choice reaction time task, in which they were instructed to respond to the appearance of a visual imperative stimulus (IS) as fast as possible, but not at the expense of accuracy. On each trial, after brief presentation of a fixation cross (200ms), participants saw a simple clock, a white circle on a black background with a black clock hand (see Figure 3.2). At trial onset, the clock hand was in the 12 o’clock position. It completed one full rotation at constant speed lasting 4000ms, irrespective of the time of presentation of the IS. The IS, a green circle or square, was presented at the centre of the screen for 200ms after a variable foreperiod (FP) since trial onset. The two ISs were mapped onto index or little finger key press responses, respectively. The mapping was counterbalanced across participants. The inter-trial interval (ITI) was sampled from a non-ageing exponential distribution (mean = 300ms) to prevent any built up of preparatory activity or temporal expectancy of trial onset or the subsequent IS during the ITI. The clock disappeared during the ITI and the screen went blank.

The clock provided participants with constant feedback about the passage of time. By providing such information, we removed ITU. In other words, this accurate external time keeper removed temporal noise arising from participants' inaccurate internal clock. In particular, we prevented the inevitable increase in ITU with longer time intervals (Gibbon, 1977). Thus, this manipulation allowed us to single out and study the effects of ETU in isolation.

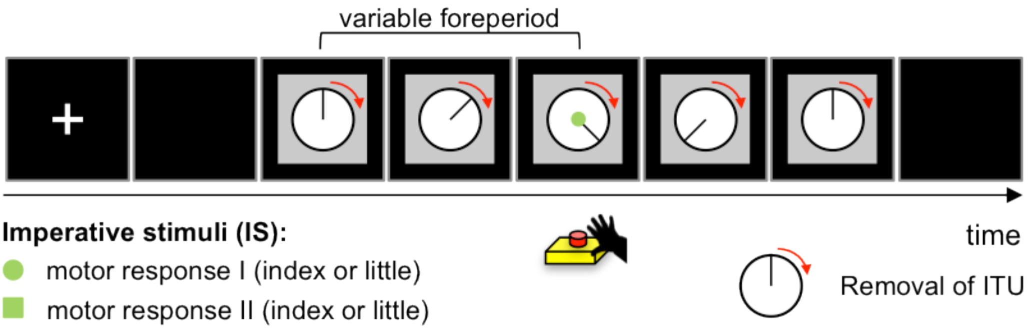


Figure 3.2: Design for Experiment 1. Participants completed a variable foreperiod choice reaction time task. After brief presentation of a fixation cross (200ms), participants saw a simple clock, a white circle on a black background with a black clock hand. The clock hand was in the 12 o'clock position at trial onset. It completed one full rotation at constant speed lasting 4000ms. As such, it provided a constant measure of time, thus removing internal temporal uncertainty (ITU). The IS, a green circle or square, was presented at the centre of the screen (200ms) after a variable foreperiod (FP). The two ISs were mapped onto index or little finger key press responses, respectively. The mapping was counterbalanced across participants. The inter-trial interval (ITI) was sampled from a non-ageing exponential distribution (mean = 300ms). The clock disappeared during the inter-trial interval. Foreperiods were sampled from continuous Gaussian distributions. External temporal uncertainty (ETU) was manipulated by varying the standard deviation of the distribution (200 / 700). The mean was fixed (2000 ms). For low event uncertainty, index finger responses were prompted on 80% of all trials. Little finger responses were prompted on the remaining 20%. For high event uncertainty, index and little finger responses were prompted on 55% and 45% of all trials, respectively. Posterior temporal uncertainty (PETU) was manipulated by including 30% of catch trials in one of the two conditions (for more information, see text). The clock completed one full turn on each trial (4000ms) thus providing a constant measure of the passage of time. This accurate external clock compensated for the noisy internal clock and removed internal temporal uncertainty (ITU).

Experimental design

Participants were exposed to eight different conditions resulting from factorially combining high and low event uncertainty (EU-, EU+), high and low ETU (ETU-, ETU+), and two hazard functions. The latter differed in how the probability of the IS developed throughout the foreperiod, which gradually reduced ETU. This factor, which in the following we will refer to as posterior external temporal uncertainty (PETU: PETU-, PETU+), was included in order to explore the possibility that the relation between event uncertainty and ETU depends on the specific type of hazard function. In addition, it allowed us to dissociate expectation and preparation from the mere passage of time. Participants thus experienced different combinations of uncertainty about the type of forthcoming action (*what; event uncertainty*), and the likely time of its execution (*when; ETU*) for two hazard functions (PETU).

All three factors, event uncertainty, ETU, and PETU, were blocked. In two sessions, separated by at least 24 hours, participants completed four blocks with all four combinations of event uncertainty and ETU with either PETU- or PETU+, respectively. The order of blocks and sessions for each participant was sampled randomly without replacement from the 24 possible permutations of the 4 blocks. In PETU-, each block consisted of 120 trials. In PETU+, each block consisted of 180 trials, of which an IS was presented in approximately 120 (70%) of these trials.

A short training of one block of 50 trials preceded each session. During training, index and little finger response were equally likely. FPs were sampled from a non-ageing exponential distribution (mean: 1500ms), to prevent participants from learning any systematic changes in IS probability throughout the FP. All FPs shorter than 488ms and longer than 3512ms were re-sampled. During training for PETU+, no IS was presented on 30% of trials. Overall, the experiment comprised two sessions of 1 (PETU-) and 1.5 hours (PETU+) each.

Event uncertainty (EU)

We manipulated event uncertainty (EU) by varying the probability of index versus little finger responses. In EU-, index finger responses were prompted on 80% of all trials (20% little finger responses), whereas in EU+, index finger responses were prompted on only 55% of all trials (45% little finger responses). Therefore, predictability of impending action varied between the two conditions, thus manipulating event uncertainty.

External temporal uncertainty (ETU)

All FPs were sampled from truncated Gaussian distributions with a mean of 2000ms. We manipulated ETU by varying the standard deviation of these Gaussians. In ETU-, the standard deviation was set to 200ms. In ETU+, standard deviation was set to 700ms. High standard deviation (ETU+) increases the variability in the time of the IS, decreasing IS predictability and thus increasing ETU. To allow sufficient time for preparation (Hackley, 2009; Hackley et al., 2009), and to preserve the symmetry of the Gaussian, the Gaussians were truncated at 488ms and 3512ms, respectively.

Posterior external temporal uncertainty (PETU)

We manipulated the probability that the IS occurs, at a given point in time throughout the foreperiod, given that is has not yet occurred (i.e. the posterior probability of the IS or the posterior external temporal uncertainty: PETU). We manipulated PETU by including trials without presentation of the IS in PETU+ (cf. dating example) and by presenting an IS on every single trial in PTEU- (cf. traffic light example). Consequently, in PETU+, after an initial increase in the probability of the IS, which peaked at the mean of the Gaussian (2000ms), IS probability decreased and it became more likely that no IS was going to be presented. By contrast, in PETU-, the posterior probability increased progressively throughout the foreperiod.

To create these distributions, we first divided the time in between the shortest (488ms) and longest FP (3512ms) in bins of 48ms (i.e. approximately three frames given a refresh rate of 60Hz) resulting in 63 time bins. We then determined the probability of the IS occurring on each bin, based on the Gaussian distribution (i.e. the probability density function) from which FPs were sampled (with the standard deviation set by the level of ETU). For PETU-, we selected one of these 63 bins according to a bin's probability of IS occurrence. Consequently, a bin closer to the mean of the Gaussian was more likely to be chosen compared to a bin towards either tail end of the distribution. The presentation of the IS was then centred on the time of the selected bin. As a consequence of this procedure, the probability of IS occurrence increased progressively throughout the foreperiod: if the IS had not yet occurred at any given point throughout the foreperiod, then it was increasingly more likely to occur.

To create PETU+, we determined, for each of the 63 bins independently, whether or not the IS would occur on that bin, based on each bin's IS probability. Consequently, the IS was more likely to occur close to the mean of the Gaussian than towards either tail end of the distribution. In addition, due to this sampling scheme, there was a proportion of trials with either no IS (~30% of trials) or multiple ISs. In the latter case, only one of the ISs was subsequently chosen with equal probability. This prevented multiple ISs within a single trial whilst preserving the shape of the underlying Gaussian. Participants were instructed to refrain from action whenever they did not receive the IS. Effectively, these trials constituted catch trials. Inclusion of catch trials caused a decrease in the probability of IS occurrence throughout the FP after a peak in probability at the mean of the Gaussian (2000ms). Put differently, the probability to receive an IS started to decrease when the foreperiod exceeded 2000ms while the probability of a catch trial increased gradually. Thus, for PETU+ the *posterior* probability of IS occurrence increased until 2000ms and declined subsequently.

Data analyses

Reaction times (RT) were calculated between the onset of the IS and the behavioural response. Responses were considered correct if the response was made after the IS (RT > 0ms) with the instructed finger. We excluded all trials with incorrect responses from the RT analyses. In addition, we excluded outliers in RT (Grubb's test).

To test for effects of event uncertainty, ETU, and posterior external temporal uncertainty on action preparation, we computed a 2 x 2 x 2 x 2 within-subject repeated measures ANOVA on mean reaction times with the following factors: (a) event uncertainty (EU-, EU+), (b) external temporal uncertainty (ETU-, ETU+), (c) posterior external temporal uncertainty (PETU-, PETU+), and additionally (d) the type of motor response (index, little finger). If a significant Mauchly's test indicated a violation of the sphericity assumption, then degrees of freedom were corrected using the Greenhouse-Geisser correction. We report partial η_p^2 as a measure of effect size. Significant interaction effects were followed-up using paired t-tests. Statistical thresholds for significance were fixed at 0.05 for all analyses and, whenever appropriate, corrected for multiple comparisons using Bonferroni correction.

Results

Overall, 14% of all trials were excluded from further analysis. 12 % were excluded due to incorrect key-presses, less than 1% due to premature responses, and 2% were classified as outliers. Response accuracy exceeded 75% in every participant.

An ANOVA on mean RTs revealed that participants responded significantly faster when the probability of the IS increased progressively (PETU-) compared to when it peaked and then declined (PETU+; $F_{(1,11)} = 25.38$, $p < 0.001$, $\eta_p^2 = 0.698$; see Figure 3). Posterior external temporal uncertainty interacted with no other experimental factors (all $p > 0.1$). Further, we found significantly faster responses for low versus high event uncertainty ($F_{(1,11)} = 7.49$, $p = 0.019$, $\eta_p^2 = 0.405$), index versus little finger responses ($F_{(1,11)} = 46.09$, $p < 0.001$, $\eta_p^2 = 0.807$), and low versus high ETU ($F_{(1,11)} = 28.25$, $p < 0.001$, $\eta_p^2 = 0.720$). Event uncertainty interacted with the type of motor response ($F_{(1,11)} = 26.79$, $p < 0.001$, $\eta_p^2 = 0.709$). Critically, the analysis revealed an interaction between event uncertainty and ETU ($F_{(1,11)} = 8.42$, $p = 0.014$, $\eta_p^2 = 0.434$). In addition, the 3-way interaction between event uncertainty, the type of motor response, and ETU was significant ($F_{(1,11)} = 5.43$, $p = 0.04$, $\eta_p^2 = 0.330$, Figure 3.3).

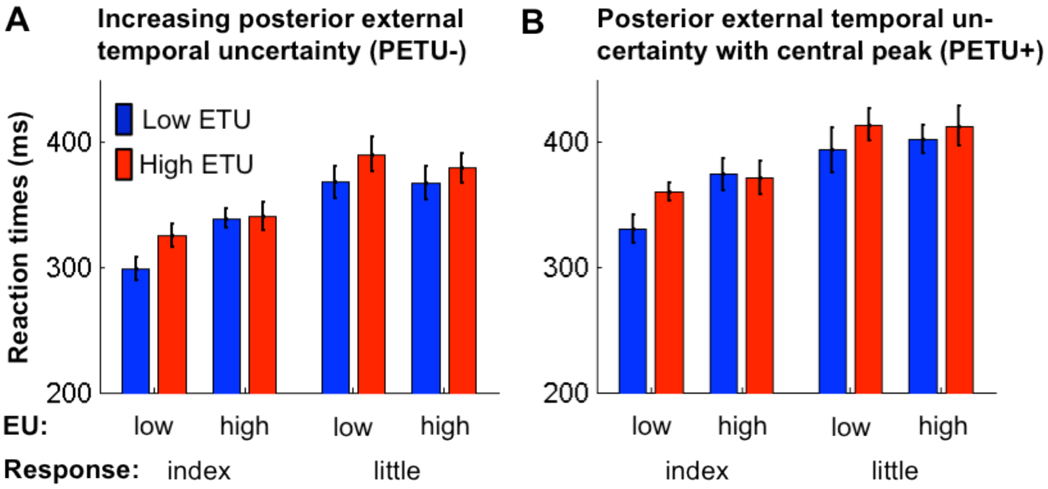


Figure 3.3: Reaction time data of Experiment 1. A. Mean reaction times for the hazard function with a progressive increase in the probability of the imperative stimulus (PETU+) and **B.** for the hazard function with the central peak (PETU-). Participants respond faster for PETU+ than PETU- but PETU did not interact with any of the other experimental variables. Responses with the less frequently prompted little finger were slower than predominant index finger responses. Low event (EU) and external temporal uncertainty (ETU) lead to faster responses. In the predominant index finger, the beneficial effect of low ETU was apparent only when event uncertainty was low, too: knowing what is a prerequisite for being able to benefit from knowing when. By contrast, responses with the less frequently prompted little finger were faster for low ETU, regardless of event uncertainty: while knowing *what* to do had no effect on little finger responses, knowing *when* to do it proved beneficial.

To explore the 3-way interaction, we collapsed across the factor PETU, and performed separate follow-up 2 x 2 within-subject repeated measures ANOVAs for each motor response (index / little finger). The ANOVA on mean reaction times for index finger responses revealed faster responses for low versus high event uncertainty ($F_{(1,11)} = 40.70$, $p < 0.001$, $\eta_p^2 = 0.787$) and low versus high ETU ($F_{(1,11)} = 18.86$, $p = 0.001$, $\eta_p^2 = 0.632$; see Figure 3.3). Critically, the interaction between event uncertainty and ETU was significant ($F_{(1,11)} = 12.72$, $p = 0.004$, $\eta_p^2 = 0.536$). This interaction was driven by a significant reduction in RTs for low versus high ETU at low event uncertainty only ($t_{(11)} = 5.98$, $p < 0.001$). At high event uncertainty, RTs for high versus low ETU did not differ ($t_{(11)} = -0.115$, $p = 0.911$).

The ANOVA on mean reaction times for little finger responses, averaged across the levels of posterior external temporal uncertainty, revealed faster responses for low versus high ETU ($F_{(1,11)} = 20.37$, $p = 0.001$, $\eta_p^2 = 0.649$). No other effects were found to be significant (all $p > 0.1$)

Thus, the follow-up analyses revealed that the 3-way interaction was caused by a significant reduction in reaction times for low versus high ETU, at low event uncertainty for the predominant motor response (i.e., index finger in the EU-condition; mean RT difference = -28.3ms, SE = 4.74). By contrast, for little finger responses, we found a reduction in reaction times for low versus high ETU for both low (mean RT difference = -21.2ms, SE = 5.75) and high event uncertainty (mean RT difference = -11.2ms, SE = 4.62). An exploratory paired post-hoc t-test, across experimental conditions, revealed that the RT benefit of low ETU for predominant index finger responses at low event uncertainty was significantly greater compared to when participants responded with the less frequently prompted little finger at high event uncertainty ($t_{(11)} = -2.26$, $p = 0.045$).

Discussion

In Experiment 1, we explored the relation between event uncertainty and ETU on action preparation for two different hazard functions whilst removing ITU. The data revealed an interaction between ETU and event uncertainty: participants responded faster when they could predict both the timing of the imperative event (low ETU) *and* the type of forthcoming motor response (low event uncertainty), at least for predominantly prompted and thus prepared index finger responses. The beneficial effect of low ETU on action preparation was not limited to the action that was prepared. Responses with the unprepared little finger still benefited from low ETU in that RTs were reduced in the same way as for prepared motor responses. Rather strikingly, however, while there was no benefit of low ETU for *prepared* actions when the type of forthcoming action was unpredictable (high event uncertainty), *unprepared* motor responses benefitted from knowing the timing of forthcoming action (low ETU) under conditions of low *and* high event uncertainty. Importantly, while absent for prepared responses, this benefit of being able to predict the timing of imperative events was reduced for unprepared responses in the face of high versus low event uncertainty. We can conclude that knowing *what* action to prepare for is a prerequisite for being able to *maximally* benefit from knowledge about *when* to execute future action. Finally, we find that while participants are generally faster when there is a monotonous increase in posterior external temporal uncertainty, there is no interaction between event uncertainty, ETU, and the development of posterior external temporal uncertainty. Thus, the relation between ETU and event uncertainty does not depend on the particular type of hazard function. While the posterior probability of the IS reduces ETU, it does not interact with temporal or event uncertainty.

Taken together, the data clearly show that, when ITU is removed, the maximal benefit of knowing *when* to act depends on knowledge about *what* action to prepare. This finding raises the question whether knowledge about the type of forthcoming action and action timing interact in the same way when the origin of temporal uncertainty is internal rather than external? We pursued this question in a follow-up experiment (Experiment 2). Importantly, in order to make Experiment 1 and 2 comparable, we sought to match levels of internal (ITU) and external (ETU) temporal uncertainty. We therefore determined the level of ITU associated with time intervals of various durations separately for each participant (Bridging Experiment: Estimating ITU) to then choose the appropriate parameters for Experiment 2.

Bridging Experiment: estimating ITU

Internal clocks do not operate at high precision; keeping track of time is difficult. Imprecision in tracking time induces ITU, which affects how we prepare for imperative events (Klemmer, 1956, 1957). Some people are better at measuring time than others (Simon Grondin & Killeen, 2009), which may lead to different preparation for action despite similar timing of imperative events. This Bridging Experiment was conducted to estimate the level of ITU, and its progressive increase with time interval duration (Gibbon, 1977; Gibbon & Allan, 1984; Rakitin et al., 1998), on a participant-by-participant basis ultimately to determine suitable foreperiod durations for Experiment 2 to manipulate ITU for each participant separately.

In Experiment 2, participants took part in a constant foreperiod choice reaction time task. We manipulated ITU by varying the duration of foreperiods across blocks: one short FP for low ITU and one long FP for high ITU (for a similar approach, see e.g. Holender & Bertelson, 1975; Klemmer, 1956; Spijkers & Walter, 1985) thus exploiting the scalar property of interval timing to manipulate ITU. We selected the short foreperiod so that its associated level of ITU was matched with the level of ETU that participants experienced in the low ETU condition in Experiment 1. We used the same strategy for the long foreperiod and high temporal uncertainty.

This allowed us to directly compare the effects of temporal uncertainty on action preparation for an internal or external origin of temporal uncertainty. To estimate ITU and its progressive increase with time interval duration on a participant-by-participant basis, we used a standard time interval production task (Lejeune & Wearden, 2006; Lewis & Miall, 2009a). We expected to find a linear increase in standard deviation with increasing time interval duration (Lejeune & Wearden, 2006). Using this linear relation, we computed appropriate foreperiods for Experiment 2 separately for each participant.

Methods

Participants

28 participants (mean age = 26.5 years, age range = 19 – 47 years, 11 males, 1 left-handed) with normal or corrected-to-normal vision took part in this study. Participants were reimbursed for time and travel (£7.50). They gave written informed consent before the experiment. This study was conducted with the approval of a local ethics committee and in line with the declaration of Helsinki.

Apparatus

The experiment was run on a desktop computer, using the cogent 2000 toolbox (http://www.vislab.ucl.ac.uk/cogent.php) running under Matlab 7.5 (Mathworks, Natick, MA). Stimuli were presented on a 19’ LCD screen with a refresh rate of 60Hz. Participants responded by pressing < space > with their right index finger on a QWERTY keyboard.

Experimental procedure & design

Participants completed a time interval reproduction task. They were instructed to reproduce one out of four target intervals (TI: 838ms, 1584ms, 2338ms, 3084ms) as accurately as possible. This interval reproduction task was conducted to estimate the level of ITU for each TI to compute one short and one long FP duration for each participant with an associated SD of 200 and 600, respectively. Note that this second value is lower than the standard deviation of the Gaussian used for high ETU in Experiment 1 (SD = 700). This is because inspection of FPs used in Experiment 1 revealed that the standard deviation of the Gaussian was described better by 600 than 700 due to the truncation of Gaussians.

We designed the current experiment to resemble Experiment 1 and 2 as closely as possible to acquire accurate estimates of the level of ITU for each TI (see Figure 3.4). This was important because accuracy in time interval estimation is sensitive to various stimulus features (Burr et al., 2009). Each trial comprised a reference phase that indicated the TI (measurement phase, see Figure 3.4), followed by the estimation phase (see Figure 3.4; we reasoned that during Experiment 2, participants can use the preceding trial as a reference to estimate the timing of the IS on the subsequent trial; Los, Knol, & Boers, 2001). Trial onset was indicated by brief presentation of a fixation cross (200ms). Following fixation, participants saw a simple clock, a white circle with a black clock hand, superimposed on a red square. The red square indicated the reference phase. The clock hand was in the 12 o'clock position at trial start, and started moving immediately back and forth in a random walk, thus not providing any information about the passage of time. We included the clock, despite it not being informative, to match the stimulus characteristics of Experiment 1 and 2. Participants were instructed to ignore the clock.

The end of the TI was marked by a green shape (circle or square, counterbalanced across subjects) briefly flashing on the screen for 200 ms. The clock disappeared after 1.5 times the TI, measured from trial onset. Then, the screen went blank for a variable time interval sampled from a non-aging exponential distribution (mean = 300ms) to prevent a progressively increasing expectancy about the onset of the measurement phase. If participants responded during the reference interval, then they received written error feedback and the reference interval was repeated.

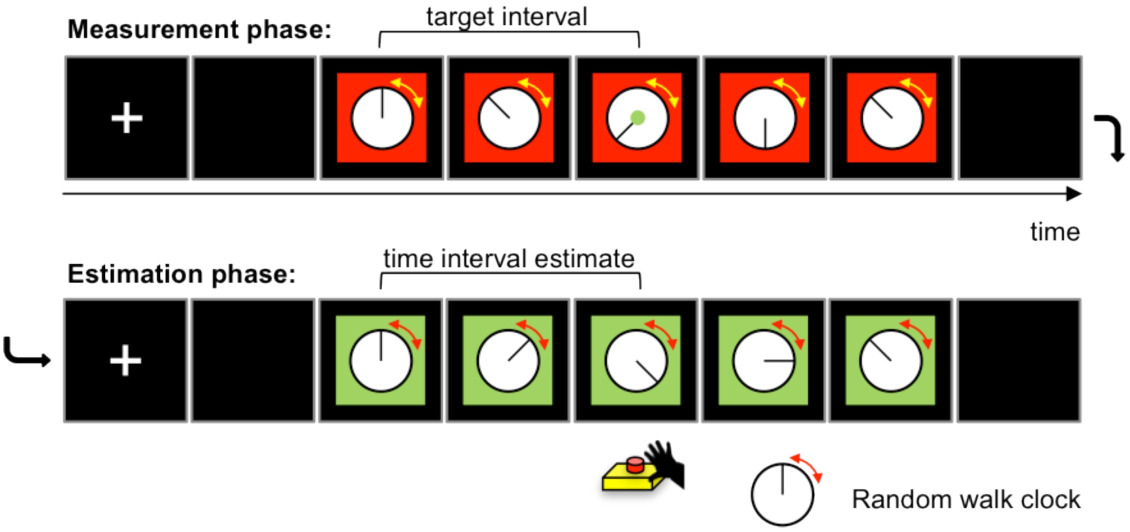


Figure 3.4: Design for the Bridging Experiment. Participants completed a time interval reproduction task. During the measurement phase (top line / red square in background), they were presented with the target interval. The start of the target interval was determined by the onset of the clock face. The end of the target interval was set by a briefly flashing circle or square (200ms; counterbalanced across subjects). During this phase, the clock was presented on red background to indicate that participants were not yet required to respond. The clock handle moved back and forth in a random walk fashion and therefore did not provide information about the passage of time or the timing of the circle or square. The clock disappeared after 1.5 times the target time interval measured from trial onset. After a variable time interval, during which the screen was blank, the clock face reappeared (bottom line). The clock was now superimposed on green background to instruct participants to respond during the estimation phase. The onset of the clock indicated the start of the target interval. With their response, participants determined the end of the target interval.

Subsequently, after brief presentation of the fixation cross (200ms), participants saw a simple clock superimposed on a *green* background, indicating the estimation phase. As before, the clock hand was in the 12 o'clock position at trial start, and started moving at the beginning of the estimation phase. Participants indicated their estimate of TI by pressing < space > with their right index finger. The clock on green background disappeared after 1.5 times the TI to allow participants sufficient time to respond, in particular when TIs were overestimated (i.e. when participants responded late). ITIs were sampled from a non-ageing exponential distribution (mean = 300ms) to prevent any build-up of expectancy about subsequent trial onset (S. Los & Schut, 2008). During the ITI the clock disappeared and the screen went blank.

Participants had to reproduce different TIs, separately in different blocks. Each block was preceded by 10 training trials to familiarise participants with a block's respective TI (Lewis & Miall, 2009a). On those training trials, participants received visual trial-by-trial feedback about their accuracy. The participant's estimate was indicated by a yellow line in relation to a red bar whose height indicated the duration of the TI. The distance and direction between the yellow line and the red bar informed participants about the magnitude and direction of bias in their time interval estimate. Following these training trials, participants completed 60 trials for each TI with summary feedback about their accuracy at the end of each block. Taken together, participants completed 4 blocks of 70 trials each.

This experiment was preceded by a short training session. Participants completed 10 trials with trial-by-trial feedback and 10 trials with summary feedback about their average time interval estimate. The only purpose of this training was to familiarise participants with the task but not to train them in reproducing a specific time interval duration. For that reason, the TI during training was the mean of the four TIs used during the experiment (1875ms). Overall, this Bridging Experiment lasted one hour.

Data Analyses

Participant's time interval estimates were computed as the time in between the start of the TI and the participant's response. Outliers in time interval estimates were excluded using Grubb's test ($\alpha = 0.05$). Then, we computed the mean and standard deviation (SD) in time interval estimates for each TI.

To test for an increase in SD with increasing TI duration, we computed a 4 x 1 within-subject repeated measures ANOVA on SD with TI as a factor (838ms, 1584ms, 2338ms, 3084ms). Then, we fitted linear regression models to SDs against respective TIs, separately for each participant. As a measure of fit, we inspected R^2 separately for each participant. We excluded participants from further analysis and participation in Experiment 2 if R^2 dropped below 0.75, which suggests a deviation from the scalar property of interval timing. We chose such a stringent criterion because the data acquired here were used to determine FPs for Experiment 2. A deviation from the scalar property of interval timing might have compromised the accuracy of chosen FPs for Experiment 2.

For remaining subjects, using the linear regression models, we predicted the two time intervals that would produce SDs of 200ms and 600ms. We excluded all participants from further analysis and participation in Experiment 2 if one of the two time intervals was shorter than 500ms or longer than 6000ms. We chose 500ms to allow sufficient time for preparation measured from trial onset, as in Experiment 1 (Hackley, 2009; Hackley et al., 2009). We chose the upper boundary of 6000ms to limit the overall duration of Experiment 2 and to reduce the likelihood to tap into different timing mechanisms that operate at a different and larger temporal scale (Mauk & Buonomano, 2004).

For the remaining participants, we tested for a bias in time interval estimation. Linear regression models were fitted to mean time interval estimates against TI duration. Regression coefficients were extracted and analysed. A regression coefficient equal to one would suggest no bias in time interval estimation. A one-sample t-test was used to test whether regression coefficients differed from one.

Results

1% of all trials was classified as outliers on the basis of time interval estimates and excluded from further analysis. We note that exclusion of outliers will affect estimates of SD, but this effect is here limited due to the small percentage of excluded outliers.

The 4 x 1 within subject repeated measures ANOVA on SD in time interval estimates revealed a significant effect of TI ($F_{(3,81)} = 41.41$, $p < 0.001$, $\eta_p = 0.611$; see Figure 3.5AB). As expected, standard deviation increased progressively with increasing TI duration ($TI_{750} – TI_{1500}$: $t_{(27)} = -4.51$, $p < 0.001$; $TI_{1500} – TI_{2250}$: $t_{(27)} = -4.79$, $p < 0.001$; $TI_{2250} – TI_{3000}$: $t_{(27)} = -4.55$, $p < 0.001$). Inspection of R^2, averaged across participants (mean = 0.77), revealed that linear regression models provided a good description of the data. We excluded seven participants because R^2-adjusted was smaller than 0.75. This was driven by a non-monotonic increase in SD with increasing TI duration thus revealing a deviation from the scalar property of interval timing.

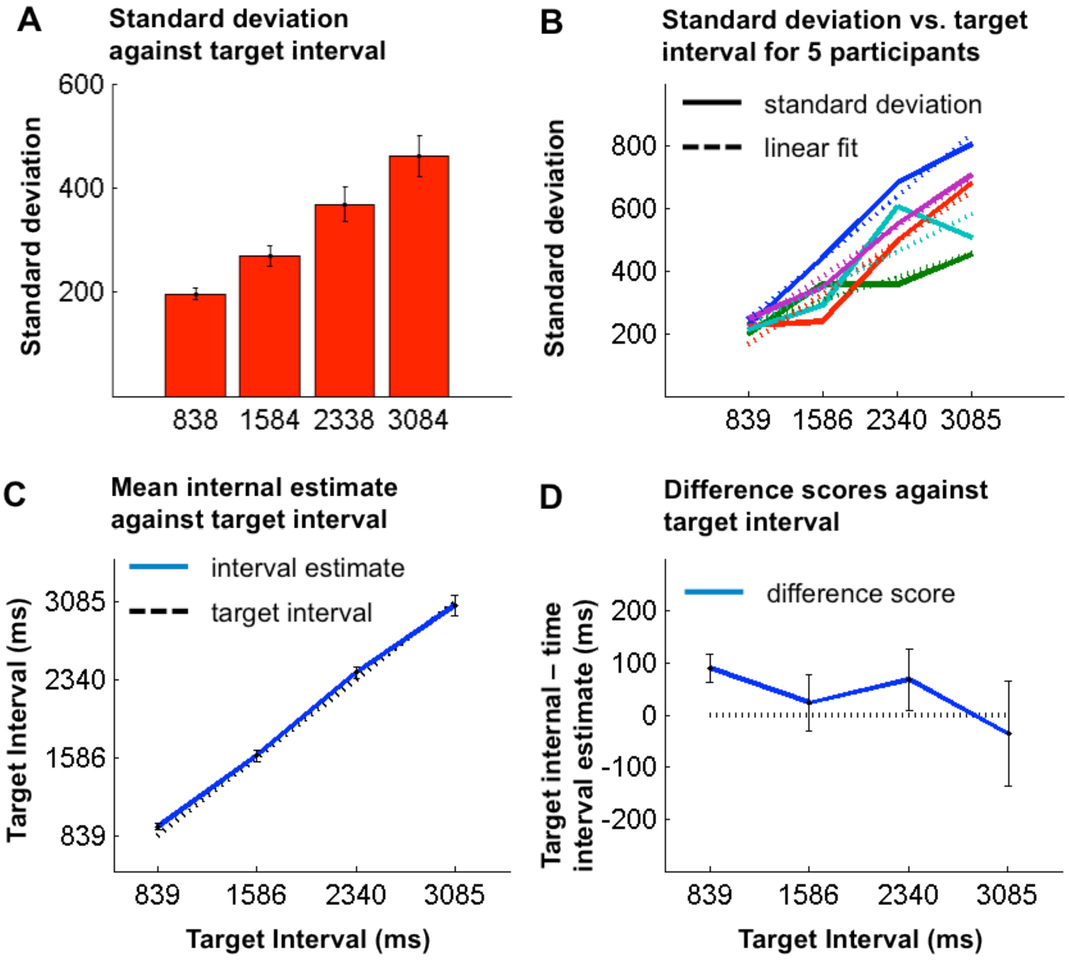


Figure 3.5: Data of Bridging Experiment. A. The standard deviation of participants' target interval estimates plotted against target interval duration averaged across all subjects. Standard deviation increased linearly with increasing target interval duration. **B.** The standard deviation of participants' target interval estimates plotted against target interval duration for 5 representative participants (solid lines) and their corresponding linear fits (dashed lines). **C.** Mean target interval estimates (solid blue line) plotted against the target interval duration (dashed black line). **D.** Difference between participants' target interval estimates and the target intervals. Participants systematically overestimated the shortest target interval and systematically underestimated the longest target interval but the magnitude of this bias was small.

Averaged across remaining participants, the time intervals associated with a SD of 200ms and 600ms were 959ms (SE = 154) and 4482ms (SE = 454), respectively. Three participants were excluded from further analysis and participation in Experiment 2 because the time interval associated with a SD of 200ms was shorter than 500ms. An additional four participants were excluded because their time interval corresponding to a SD of 600ms was longer than 6000ms. Thus effectively, the first 3 participants were excluded because they were too noisy, and the latter four because they were too accurate in time interval estimation. After exclusion of these participants, the time intervals associated with an SD of 200ms and 600ms were 1046ms (SE = 84.6) and 3695ms (SE = 324), respectively, averaged across participants.

A one-sample t-test on regression coefficients (mean = 0.93, SE = 0.04), extracted from the linear model on mean time interval estimates against target interval duration, revealed a significant bias in time perception ($t(14) = 25.46$, $p < 0.001$; see Figure 3.5CD). This bias, however, was qualitatively small: on average, participants' time interval estimates deviated by 8.23%, 0.87%, 0.04%, and -1.57%, respectively, from the respective TIs.

Discussion

This Bridging Experiment was conducted to estimate participants' ITU expressed by their variability in time interval reproduction. We predicted a linear increase in standard deviation of reproduced time intervals with increasing target interval duration. Indeed, the standard deviation increased progressively with increasing target interval duration. In 21 out of 28 participants, this relation was described well by a linear model. Using this linear relationship, we estimated two time intervals for each participant separately associated with a standard deviation of 200 and 600. Six participants were too noisy or too accurate in time interval estimation and had to be excluded because their estimated foreperiods were too short or too long, respectively. Thus, 15 participants qualified to participate in Experiment 2.

The data furthermore show a small but systematic bias in time perception. Participants systematically overestimated time intervals shorter and underestimated time intervals longer than the mean target interval (i.e. regression towards the mean; Jazayeri & Shadlen, 2010). However, although significant, the bias turned out to be small. The standard deviation therefore provided an adequate description of participants' ITU. The estimated time intervals associated with a standard deviation of 200ms and 600ms thus reliably manipulated ITU in Experiment 2 and guaranteed that Experiment 1 and 2 were matched in level but not origin of temporal uncertainty.

Experiment 2

Does it matter, for the relation between event and temporal uncertainty, whether temporal uncertainty originates from an unpredictable world (ETU) or noisy time perception (ITU)? We addressed this question in Experiment 2. Experiment 1 revealed that, when temporal uncertainty was induced by an unpredictable world, knowledge about what action to prepare for is a prerequisite to (maximally) benefit from being able to predict the timing of future action. Does this relation between event and temporal uncertainty change when temporal uncertainty comes instead from noisy time perception? Participants may be able to compensate for high ITU, due to life-long experience with their own noisy time perception, which in turn may alter the relation between event and temporal uncertainty. Perhaps, the ability to compensate depends on at least being able to predict the type of forthcoming motor action?

To explore these questions, we used a constant foreperiod choice reaction time task in which one short (low ITU) and one long (high ITU) foreperiod were selected for each participant individually, based on the results of the Bridging Experiment. This ensured that levels of internal (ITU; Experiment 2) and external temporal uncertainty (ETU; Experiment 1) were comparable across experiments.

Based on Experiment 1 and previous work (Holender & Bertelson, 1975; Spijkers, 1990; Spijkers & Walter, 1985), three alternative hypotheses were conceivable: (i) the origin of temporal uncertainty does not modulate the relation between temporal and event uncertainty. In other words, the interaction between ITU and event uncertainty is comparable to the interaction between ETU and event uncertainty (i.e. maximal benefit of low ITU under conditions of low event uncertainty). Alternatively, the origin of temporal uncertainty may matter for the relation between temporal and event uncertainty. (ii) ITU and event uncertainty may have independent effects on action, as previously reported (Holender & Bertelson, 1975; Spijkers, 1990; Spijkers & Walter, 1985); or (iii) the interaction between ITU and event uncertainty may be qualitatively different from the one reported in Experiment 1: for example, while participants may be able to compensate for high ITU when they know which action to prepare for, they may suffer from high ITU when the type of future action is unpredictable. This latter option could explain why, given our findings of Experiment 1, previous studies on the relation between event and temporal uncertainty have found additive effects of temporal and event uncertainty on action preparation. In these studies, when participants experienced both ETU and ITU in conjunction. In this case, if Hypothesis 3 turns out to be true, effects of ETU and ITU would cancel each other out. For that reason, given findings of Experiment 1, we here adopt the third hypothesis.

Methods

Participants

We re-invited all 15 participants who satisfied the criteria of the Bridging Experiment to participate in Experiment 2. One participant did not respond to our invitation. Thus, 14 participants (mean age = 26.9 years, age range = 20 – 47 years, 6 males, 1 left-handed) took part in Experiment 2. Participants were reimbursed for time and travel (£10). They gave written informed consent before participation. This study was conducted with the approval of a local ethics committee and in line with the declaration of Helsinki.

Apparatus

The experiment was run on a desktop computer, using the cogent 2000 toolbox (http://www.vislab.ucl.ac.uk/cogent.php) running under Matlab 7.5 (Mathworks, Natick, MA). Stimuli were presented on a 19' LCD screen with a refresh rate of 60Hz. Participants responded by pressing right < AltGr > and < Ctrl > keys with their right index and little finger, respectively, on a standard QWERTY keyboard.

Experimental procedure

Participants completed a constant FP choice reaction time task in which they were instructed to respond to the appearance of an imperative stimulus (IS) as fast as possible but not at the expense of accuracy (see Figure 3.6). Participants experienced two levels of event uncertainty (EU-, EU+) and two levels of internal temporal uncertainty (ITU-, ITU+). Posterior external temporal uncertainty (PETU) was not manipulated in Experiment 2. A *constant* FP choice reaction time task does not allow manipulation of posterior external temporal uncertainty.

The constant FP choice reaction time task resembled the variable choice reaction time task in all aspects except for (a) FP duration (see below) and (b) the information provided by the clock (see Figure 3.6). In Experiment 1 the clock removed ITU, whereas in Experiment 2, the clock did not provide information about the passage of time. The clock hand was in the 12 o'clock position at trial start. It started moving back and forth in a random walk fashion. Participants received the imperative stimulus (IS), a circle or square prompting index or little finger responses, respectively after a constant FP. The clock hand continued to move back and forth until 1.5 times the FP measured since trial start. The clock disappeared and the screen went blank thereafter. After an ITI, sampled from a non-ageing (exponential) distribution (mean = 300ms) participants continued with the next trial.

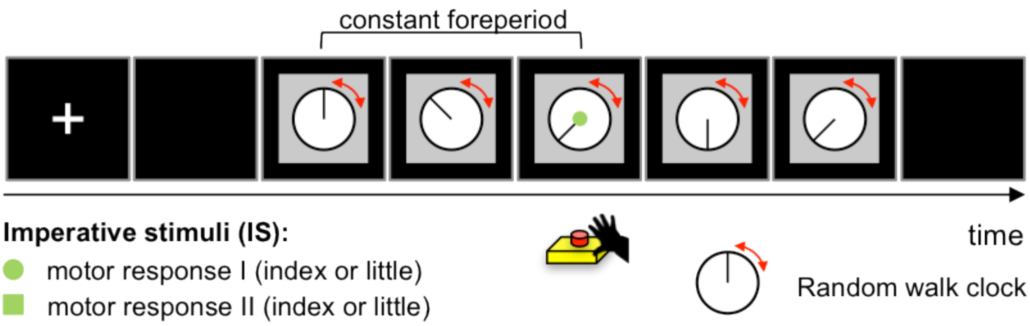


Figure 3.6: Design of Experiment 2. Participants completed a constant foreperiod 2-choice reaction time task. The imperative stimulus (IS) occurred after a short foreperiod (low internal temporal uncertainty; ITU) or long foreperiod (high ITU). The duration of these two foreperiods was determined on a subject-by-subject basis based on the results of the bridging experiment. The short foreperiod was associated with a standard deviation of 200 and the long foreperiod with a standard deviation of 600. For low event uncertainty, index finger responses were prompted by the IS on 80% of all trials. Little finger responses were prompted on the remaining 20%. For high event uncertainty, index and little finger responses were prompted on 55% and 45% of all trials, respectively. The clock handle moved back and forth in a random walk thus not providing information about the passage of time or the timing of the IS.

Experimental design

Participants were exposed to four different experimental conditions created by combining high and low event uncertainty (EU-, EU+) with high and low ITU (ITU-, ITU+) in a 2 x 2 factorial design. The factors event uncertainty and ITU were blocked. Participants completed 4 block each 120 trials. Before the experiment, participants took part in a short training session of one block of 50 trials. The FP used during training was the mean of the two FPs using during the experiment.

Event uncertainty (EU)

Event uncertainty was manipulated as in Experiment 1. In EU-, index finger responses were prompted on 80% of all trials (20% little finger responses). In EU+, index finger responses were prompted on 55% of all trials (45% little finger responses).

Internal temporal uncertainty (ITU)

The level of internal temporal uncertainty was manipulated by choosing a short (ITU-) and a long (ITU+) constant FP. The duration of the short and long FP was estimated for each participant separately (see Bridging Experiment) so that the short FP would be associated with a SD of 200ms, and the long FP with a SD of 600ms. In this way, the ITU levels in Experiment 2 were matched to the two levels of ETU in Experiment 1. The short FP averaged across participants was 936ms (SE = 83) and the long FP 3643ms (SE = 305).

Data analysis

Reaction times (RT) were calculated between the onset of the IS and the behavioural response. Responses were considered correct if the response was made after the IS (RT > 0ms) with the instructed finger. We excluded all trials with incorrect responses (e.g. index finger responses when the little finger was prompted) from further analyses. In addition, we excluded trials with outlying reaction times (Grubb's test, $\alpha = 0.05$).

We directly compared the data acquired in the present experiment, where temporal uncertainty had an internal origin, to the data from Experiment 1 (only PETU- to match experiments in that an IS occurred on each trial), where the origin of temporal uncertainty was external. We computed a 2 x 2 x 2 x 2 mixed between-within subjects ANOVA on mean reaction times with the origin of temporal uncertainty as a between-subject factor (external / internal) and event uncertainty (EU-, EU+), the level of temporal uncertainty (TU-/TU+), and the type of motor response (index, little) as within subject factors. If Mauchly's test indicated a violation of the sphericity assumption, then degrees of freedom were corrected using Greenhouse-Geisser. We report partial η_p^2 as measures of effect size. Significant effects were further explored using paired t-tests. Statistical threshold was fixed at 0.05 for all analyses and, whenever appropriate, corrected for multiple comparisons using Bonferroni corrections.

Results

Data from two participants were excluded from further analysis as their total number of errors exceeded 25% of all trials. Of the remaining 12 participants, 11.4% of all trials were excluded from further analysis due to incorrect key-presses, less than 1% due to premature responses. 2% were classified as RT outliers.

The 2 x 2 x 2 x 2 mixed between-within subjects ANOVA on mean reaction times revealed that participants responded faster under conditions of external compared to internal temporal uncertainty ($F_{(1,22)} = 4.43$, $p = 0.047$, $\eta_p^2 = 0.168$; see Figure 3.7). Further, responses were faster with the index finger ($F_{(1,22)} = 64.26$, $p < 0.001$, $\eta_p^2 = 0.745$), for low versus high event uncertainty ($F_{(1,22)} = 5.09$, $p = 0.034$, $\eta_p^2 = 0.188$), and for low versus high temporal uncertainty ($F_{(1,22)} = 4.83$, p 0.039, $\eta_p^2 = 0.180$). In addition, we found a significant 2-way interaction between event uncertainty and the type of motor response ($F_{(1,22)} = 20.19$, $\eta_p^2 = 0.479$) and, crucially, a significant 3-way interaction between event uncertainty, the level of temporal uncertainty, and the origin of temporal uncertainty ($F_{(1,22)} = 14.12$, $p = 0.001$, $\eta_p^2 = 0.391$).

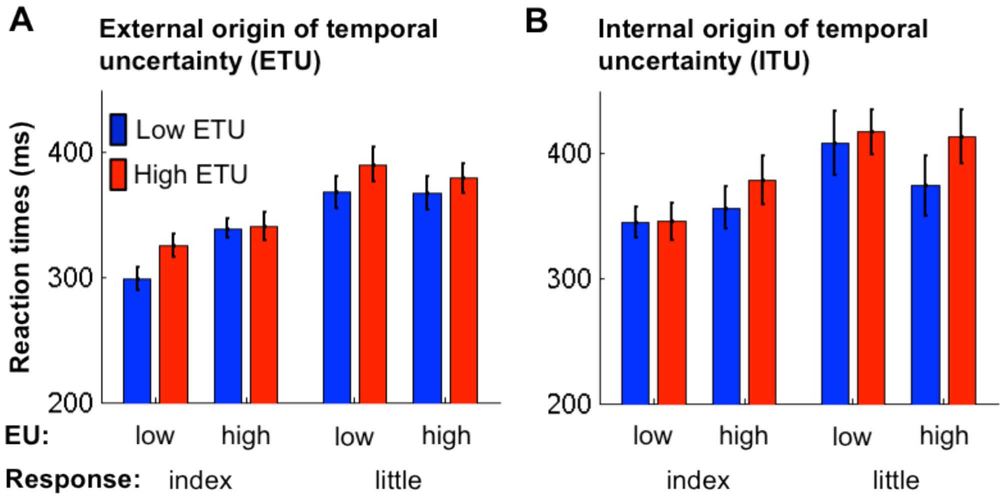


Figure 3.7: Reaction time data of Experiment 2. A. The data of Experiment 1 for progressively increasing posterior temporal uncertainty (PETU+). These data were compared directly to the data of Experiment 2. **B**. The data revealed that the relation between event and temporal uncertainty depends on the origin of temporal uncertainty. When the origin of temporal uncertainty is external (ETU), then one has to know what to do to benefit from knowing when to do it. By contrast, when the origin of temporal uncertainty is internal (ITU), then not knowing when has a detrimental effect only when the information about what to do is limited, too (high event uncertainty). When participants know what action to prepare for, they may be able to compensate for high ITU.

The significant 2-way interaction between event uncertainty and the type of motor response was driven by a reduction in RT for low versus high event uncertainty for index finger responses only ($t_{(11)}$ = -5.13, p < 0.001) while there was no difference between high versus low event uncertainty for little finger responses ($t_{(11)}$ = 1.13, p = 0.282; see Figure 3.7).

We further explored the significant 3-way interaction by computing two 2 x 2 within subject repeated measures ANOVAs separately for ETU and ITU averaged across the type of motor response. For ITU, the follow-up ANOVA revealed a significant interaction between event uncertainty and temporal uncertainty ($F_{(1,11)}$ = 6.80, p =0.024, η_p^2 = 0.382). This interaction was driven by an increase in reaction times for high versus low ITU at high event uncertainty approaching the boundary of significance ($t_{(11)}$ = -2.13,p = 0.056; see Figure 3.7). There was no difference in reaction times for high versus low ITU at low event uncertainty ($t_{(11)}$ = 0.29, p = 0.774).

For ETU, the ANOVA revealed a significant main effect of temporal uncertainty ($F_{(1,11)} = 26.34$, $p < 0.001$) and a significant interaction between temporal and motor uncertainty ($F_{(1,11)} = 10.50$, $p = 0.008$). This interaction was driven by a significant reduction in RTs for low versus high ETU at low event uncertainty only ($t_{(11)} = -5.48$, $p < 0.001$; see Figure 3.7). At high event uncertainty, the reduction in RTs was marginally significant ($t_{(11)} = -1.84$, $p = 0.093$). These results correspond with the findings of Experiment 1 where the same data were analysed separately for index and little finger responses but averaged across the levels of posterior external temporal uncertainty.

Thus, the 3-way interaction revealed that the interaction between temporal and event uncertainty depends on the internal or external origin of temporal uncertainty. For ITU, we found a marginally significant beneficial effect of low temporal uncertainty only when participants could not predict the type of forthcoming motor response at high event uncertainty. By contrast, for ETU, we found a significant beneficial effect of low ETU on RTs only when the type of forthcoming motor action was predictable at low event uncertainty.

Discussion

We here asked whether the *source* of temporal uncertainty, that is an unpredictable world (ETU) or noisy time perception (ITU), determines whether event and temporal uncertainty interact. In line with our predictions, we indeed found that the origin of temporal uncertainty determines the interaction between temporal and event uncertainty. For ETU, there is a beneficial effect of low temporal uncertainty but only when the type of forthcoming motor action is predictable (i.e. low event uncertainty). For ITU, participants can compensate for the detrimental effect of high ITU on action preparation but only when forthcoming motor actions are predictable (i.e. low event uncertainty). When event uncertainty is high, action preparation is detrimentally affected by high ITU and responses are slower. These findings reveal, for the first time, a fundamental difference in the influence of ETU and ITU on action preparation under conditions of event uncertainty.

The effects of temporal uncertainty, both ETU and ITU, are not restricted to the action that was prepared (i.e. predominant index finger responses). Unprepared index finger responses were slower but the modulation of reaction times by event and temporal uncertainty followed the same pattern as for prepared motor responses. Two distinct preparatory processes thus support temporal and event preparation: event preparation is selective for prepared motor action while temporal preparation is non-selective but transient. Importantly, the data reveal that these two preparatory processes are influenced by the *origin* of temporal uncertainty.

General discussion

The experiments presented in this chapter address whether the *origin* of temporal uncertainty determines how temporal and event uncertainty interact. In other words, does it matter for preparation for action whether temporal uncertainty arises from an unpredictable world (ETU) or, alternatively, from noisy time perception (ITU). And if so, how does this impact on whether one can benefit from knowing *what* action to prepare for when action timing is unknown and vice versa?

Summary of results

The present data reveal that the relation between temporal und event uncertainty indeed depends on the origin of temporal uncertainty: when temporal uncertainty is caused by an unpredictable world (ETU) then action preparation benefits from low temporal uncertainty only when one knows *what* action to prepare for (i.e. low event uncertainty). By contrast, participants can compensate for high

ITU, but only when impending motor actions are highly predictable (i.e. low event uncertainty). When impending motor actions are less predictable (i.e. high event uncertainty), then action preparation is detrimentally affected by high ITU.

The effects of ETU, ITU, and event uncertainty on action preparation are not limited to the predicted and thus prepared actions. Less frequently prompted (and thus unprepared) actions also benefit, to a comparable extent, from low ETU when the type of forthcoming action is predictable (i.e. low event uncertainty; with one exception which we discuss below). Similarly, preparation for action is impaired by high ITU under conditions of high event uncertainty for prepared *and* unprepared motor actions. These data thus support the proposal that preparation for *what* to do (i.e. event preparation) and *when* to do it (i.e. temporal preparation) engage two distinct preparatory processes (Bertelson & Boons, 1960; Holender & Bertelson, 1975; Sanders, 1990; Spijkers, 1990; Spijkers & Walter, 1985). Event preparation is selective for the prepared action and explains faster responses for prepared motor actions. By contrast, temporal preparation is non-selective for the type of action: both frequently and less frequently prompted actions are affected to the same extent by ETU and ITU. Event preparation can be maintained over time, which is why it is not affected by information about *when* to act (i.e. ETU or ITU). Temporal preparation, on the contrary, is transient (i.e. difficult to maintain over time; see Alegria, 1974; Gottsdanker, 1975). Consequently, knowing *when* to act improves action preparation.

Two strategic adjustments in preparation: the certainty & the strategy effect

Importantly, our data reveal that the origin of temporal uncertainty affects the preparatory processes that underlie both event and temporal preparation, respectively. The relation between ETU, ITU, and event uncertainty can be accounted for by two (or three, see below) strategic adjustments in action preparation under conditions of event uncertainty and either ETU or ITU (see Figure 8). First, temporal preparation may be modulated by event uncertainty: when actions are less predictable (i.e. high event uncertainty) then the time interval decreases across which preparation can be maintained (*certainty effect).* Second, there may be a change in strategy when preparing for action under conditions of ETU compared to ITU (*strategy effect*). By definition, when participants experience ETU, the timing of the imperative stimulus varies from one instance to the next. Participants attempt to align preparation with the (their estimated) likely timing of the imperative event. In order to do so, participants give particular weight to the timing of the immediately preceding imperative stimulus as a temporal cue for subsequent preparation (Alegria & Delhaye-Rembaux, 1975; Bertelson, 1967; Bertelson & Tisseyre, 1968; Drazin, 1961; Los et al., 2001; Steinborn, Rolke, Bratzke, & Ulrich, 2008; Vallesi & Shallice, 2007; Van der Lubbe, Los, Jaśkowski, & Verleger, 2004). By contrast, ITU is induced by inaccurate time perception. The *objective* timing of imperative events does not vary. Previous studies have revealed that participants can compensate for *subjective* timing variability induced by inaccurate time perception (Balci et al., 2009; Hudson et al., 2008). This entails that participants know, to some extent, that they induce (subjective) timing variability. Consequently, instead of using their *subjective* estimate about the timing of the IS on the *preceding* trial, participants might align their preparation with their best *current* (but noisy) subjective estimate about the timing of the IS (Figure 3.8DE).

This change in strategy (i.e. the *strategy effect*), together with the *certainty effect*, can account for the interaction between ETU, ITU, and event uncertainty (see Figure 3.8). In general, given a fixed time interval across which preparation can be maintained (i.e. the preparatory interval, see Figure 8A), responses to imperative events are less likely to benefit from preparation when temporal uncertainty is high, regardless of its origin (Figure 3.8C). Importantly, for comparable levels of temporal uncertainty, due to the *strategy effect*, preparation is less likely to coincide with the IS under conditions of ETU, compared to ITU (Figure 3.8BC) because participants are trying to “chase up” the imperative event by taking the timing of the IS on the *preceding* trial as a temporal cue for preparation on the subsequent trial. Consequently, the timing of participants’ preparatory interval will vary from trial to trial more strongly for preparation under conditions of ETU than ITU. Participants are therefore more likely to be *un*prepared when the IS occurs under conditions of ETU, compared to ITU (see Figure 3.8BC), because they were prepared at the wrong moment in time.

In addition, when event uncertainty is high, participants are less likely to be prepared when the IS occurs, under conditions of ETU and ITU, due to the *certainty effect*. Figure 8D illustrates that there is a preparatory interval that maximises the difference in the probability to be prepared when the IS occurs between low and high ETU (or low and high ITU). This difference decreases on either side of this “maximising” preparatory interval, with a steeper slope for increasingly shorter preparatory intervals, and for preparation under conditions of ITU to either side. The specific preparatory interval for low and high event uncertainty may then determine (the direction of) the difference in the probability to be prepared when the IS occurs for high and low ETU and ITU. For a variety of preparatory intervals, this difference between high and low ETU will be larger for low compared to high event uncertainty (see Figure 3.8D for an example), in agreement with observed differences in reaction times. And for the *same* variety of preparatory intervals, this difference between high and low ITU will be smaller for low compared to high event uncertainty (see 3.8D for an example), again in agreement with the reaction times observed in this study. As such, the relation between event, temporal, and the origin of temporal uncertainty can be explained by two adjustments in preparation: the *certainty effect* and the *strategy effect*. While the former reveals that temporal preparation is sensitive to information about the forthcoming type of motor action, the latter reveals a fundamental difference in preparation for action under conditions of ETU versus ITU (i.e. a change in strategy).

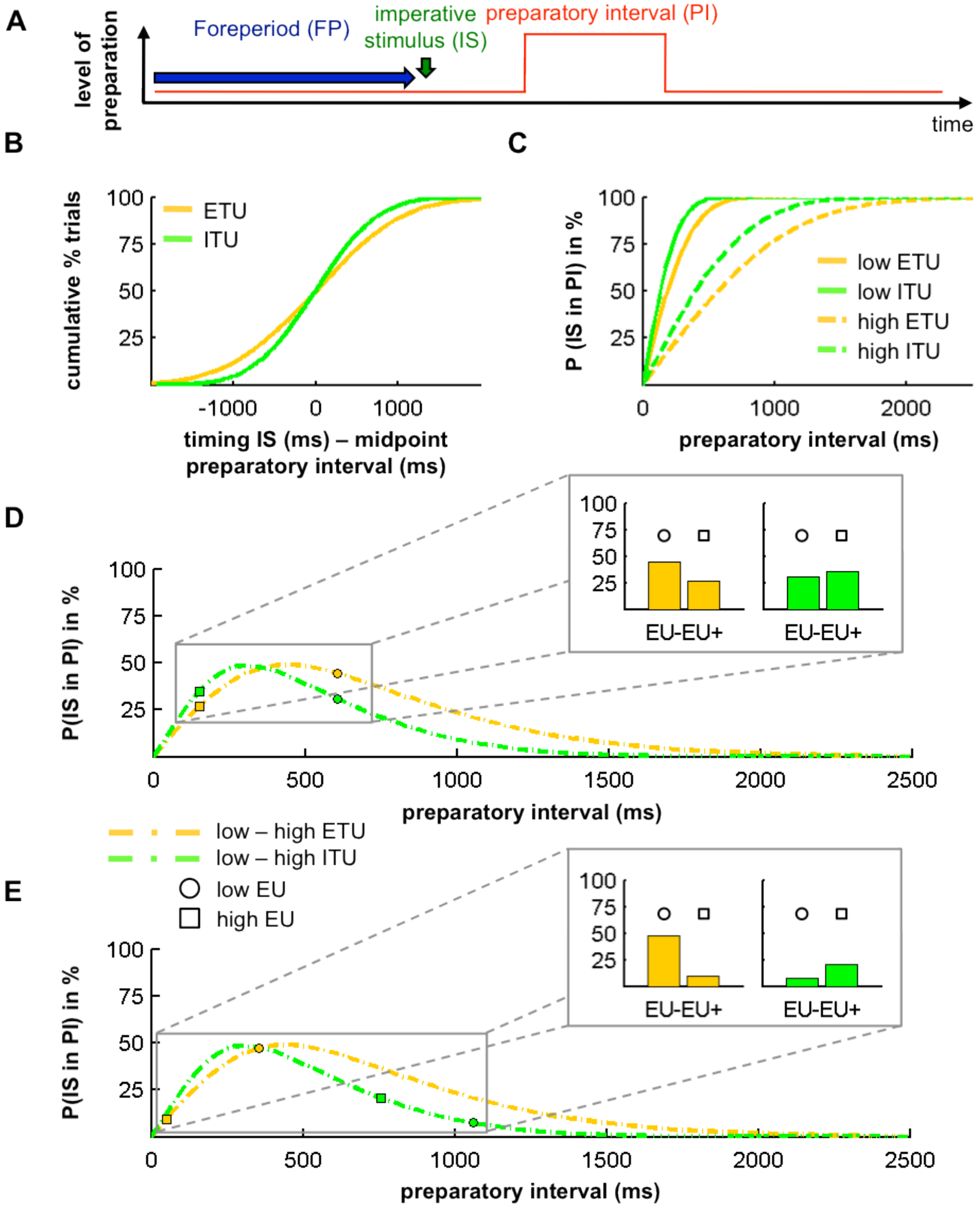


Figure 3.8: The interaction between ETU, ITU, and event uncertainty. The interaction between event, temporal, and the origin of temporal uncertainty may arise from (i) a decrease in the duration of the time interval across which preparation can be maintained for high versus low event uncertainty (*certainty effect*), (ii) a change in strategy when preparing for actions under conditions of external (ETU) versus internal temporal uncertainty (ITU; *strategy effect*), and potentially (iii) an increase in the duration of the preparatory interval for internal (ITU) versus external temporal uncertainty (ETU) that compensates for internally generated temporal noise (*compensation effect*). The plots in **B-E** show simulated effects of these different preparatory adjustments on the level action preparation that can occur when exposed to combinations of high and low event uncertainty (EU), external temporal uncertainty (ETU), or internal temporal uncertainty (ITU). Simulated effects were obtained by sampling 10.000 foreperiods from two Gaussians (mean: 2000ms; standard deviation: 200 for low temporal uncertainty, 600 for high temporal uncertainty). We assumed that variability was either externally induced (ETU; orange) or originated from inaccurate internal clocks (ITU; green). The interaction between event, temporal, and the origin of temporal uncertainty can be explained by the *certainty* and *strategy effect* alone, see D. However, adding the *compensation effect* accounts for more specific differences in observed reaction times (see E).

A. The foreperiod (FP) is the time interval in between trial onset and the occurrence of the imperative stimulus (IS). The preparatory interval is the time interval across which preparation can be maintained. For simplicity, in the current simulation, the preparatory interval has a sudden on- and offset. We note that assuming a more a gradual on- and off-set (e.g. a bell-shaped preparatory interval) would not substantially change the influence of the *certainty*, *strategy*, and *compensation effect* on action preparation.

B. Under conditions of ETU, participants use the timing of the IS on the previous trial as a temporal cue for action preparation on the subsequent trial. Under conditions of ITU, participants align preparation according to their subjective but noisy estimates about current foreperiod duration. This difference lies at the heart of the *strategy effect*: when matching the level of temporal uncertainty (here: high temporal uncertainty, SD = 600) and the duration of the preparatory interval (here: 300ms), preparation is more likely to be misaligned with the timing of the imperative event under conditions of ETU compared to ITU. In more formal terms, the difference in time between the mid-point of the preparatory interval and the IS (x-axis) is on average greater for ETU compared to ITU. Here, this is reflected by a higher standard deviation in the cumulative frequency (y-axis) distribution of the difference in time between the mid-point of the preparatory interval and the timing of the imperative event (x-axis). **C.** The probability, *P* (in %; y-axis) that the IS falls into the preparatory interval, shown for conditions of ETU (orange) and ITU (green) for a range of preparatory intervals (in ms; x-axis). Participants are more likely to benefit from preparation when temporal uncertainty is low (bold lines), regardless of the origin of uncertainty, and when the preparatory interval is long.

D. The difference in probability (in %, y-axis) between high and low internal (green) and external (orange) temporal uncertainty (cf. C: the difference between solid and dashed lines). The difference between high and low temporal uncertainty increases, peaks, and then slowly tapers off with increasing duration of the preparatory interval. The difference between high and low temporal uncertainty thus depends on the duration of the preparatory interval for both ETU and ITU. It is small when the preparatory interval is extremely short or long, while it is comparatively large for intermediate values. This has significant impact on how subjects deal with event, temporal, and the origin of temporal uncertainty. A relatively short preparatory interval for high event uncertainty (*certainty effect*), and conversely a long interval for low event uncertainty, can explain the increase in reaction times for high compared to low *ETU* under conditions of low event uncertainty (EU-) and the increase in reaction times for high compared to low *ITU* under conditions of high event uncertainty (EU+), respectively. Here, two preparatory intervals were chosen for which this observed relation between event, temporal, and the origin of temporal uncertainty holds. The bar graphs show the difference in probability that the imperative event is going to benefit from preparation for action (i.e. that the preparatory interval coincides with the timing of the IS) for low minus high temporal uncertainty. A bigger difference in probability will translate into a bigger difference in reaction times. This illustrates that the *certainty effect* and the *strategy effect* can explain the interaction between event, temporal, and the origin of temporal uncertainty. In agreement with observed reaction times, the difference in probability is larger for high versus low ETU under conditions of low event uncertainty (EU-) and high versus low ITU under conditions of high event uncertainty (EU+).

E. Adding the *compensation effect* to the *strategy*, and *certainty effect* removes the restriction that preparatory intervals must be comparable for ETU and ITU. Preparatory intervals are longer for ITU because participants increase the time interval across which preparation is maintained, at the expense of the overall strength of preparation, to be at least somewhat prepared when the IS occurs. The difference in the duration of the preparatory interval between high and low event uncertainty, however, is comparable for ETU and ITU (i.e. the *certainty effect* does not interact with the *compensation effect*). Adding the *compensation effect* can account for no difference in reaction times for low versus high ETU under conditions of high event uncertainty (EU+) and no difference in reaction time for low versus high ITU under conditions of low event uncertainty (EU-).

A third strategic adjustment in preparation: the compensation effect

Participants may further attempt to compensate for high ITU (cf. Balci et al., 2009; Hudson et al., 2008) by directly adjusting the duration of the time interval across which preparation is maintained (*compensation effect*). This may come at the expense of the overall strength of preparation (Figure 3.8E). In other words, participants may compensate for high ITU by maintaining preparation across a longer time interval to ensure at least some level of preparation when the IS actually occurs. In comparing Figure 3.8D to Figure 3.8E, one can see that the *compensation effect* removes the restriction that preparatory intervals for high and low event uncertainty must be comparable for ETU and ITU. Instead, preparatory intervals are longer for ITU while the *difference* in preparatory intervals for high compared to low event uncertainty remains comparable for both types of temporal uncertainty (i.e. the size of the *certainty effect* does not depend on the origin of temporal uncertainty). Adding this *compensation effect* can account for the observed increase in reaction times for high versus low ETU under conditions of low event uncertainty (EU-) while there was no detectable reaction time difference when event uncertainty was high (EU+). Similarly, while we found no difference between high and low ITU for low event uncertainty (EU-), reaction times increased for high versus low ITU when event uncertainty was high (EU+). Further, the *compensation effect* in combination with the *strategy* and *certainty effect* can also account for a smaller difference in reaction times under conditions of ITU (i.e. the difference between high versus low temporal uncertainty for high versus low event uncertainty) compared to ETU. Finally, the compensation effect also explains slower reaction times under conditions of ITU in general. We thus propose that three adjustments in action preparation (described here by the *certainty effect*, *strategy effect*, and *compensation effect)* can account for the complex relationship between event and temporal uncertainty.

The certainty, strategy, and compensation effect in context

Our results suggest that preparation for *when* to act (*temporal uncertainty*) is influenced by advance information about *what* to do (*event uncertainty*) and that this interaction depends on whether temporal uncertainty arises from an unpredictable world (ETU) or noisy time perception (ITU). Notably, other studies have not observed such dependencies (Cotti et al., 2011; Holender & Bertelson, 1975; Sakai et al., 2000; Spijkers, 1990; Spijkers & Walter, 1985). We note, however, that such studies did not distinguish between the two different sources of temporal uncertainty that we here identified. Our results show that when participants experience both ETU and ITU in conjunction, then reaction time differences “cancel each other out”. In other words, previous studies failed to find the interaction between event and temporal uncertainty, which is modulated by the temporal uncertainty’s origin, because they failed to pay attention to the difference between ETU and ITU. Future studies should distinguish between the external and internal origin of temporal uncertainty: even if levels of noise are comparable, it matters where this noise comes from.

But our findings agree with previous studies in that there are two preparatory processes underlying preparation for action: one underlying *what* to do and one underlying *whe*n to do it (Holender & Bertelson, 1975). Our data reveal that preparation for *when* is affected by information about *what* to, that participants adjust temporal preparation according to the origin of temporal uncertainty that they experience, and compensate for their own internal temporal noisiness (ITU).

Conclusions

The present study reveals that external and internal temporal uncertainty have fundamentally different effects on action preparation under conditions of event uncertainty. When temporal uncertainty arises from an unpredictable world (ETU), then participants can benefit from knowing *when* to act only when they also know *what* type of action to prepare for. When temporal uncertainty is due to noisy time perception (ITU), participants can compensate for high ITU as long as they know which action to prepare for. These findings can be explained by two, possibly three strategic adjustments in preparation: (i) participants can maintain preparation for longer when they know *what* action to prepare for (*certainty effect*); (ii) under conditions of ETU, participants use the timing of the IS on the preceding trial as a temporal cue for subsequent preparation whereas, under conditions of ITU, participants use their current subjective but noisy estimate about IS timing (*strategy effect*); (iii) finally, participants compensate for ITU by increasing the time interval across which preparation is maintained at the expense of the overall strength of preparation (*compensation effect*). Both the *strategy* and *compensation effect* reveal that the origin of temporal uncertainty matters for the effect of temporal uncertainty on preparation for action. These effects thus reveal an important and fundamental difference between ETU and ITU: even when levels of temporal noise are comparable, effects on behaviour differ when their source is different.

Chapter 4: Event preparation is modulated by advance information about action timing

Abstract: Studies using Transcranial Magnetic Stimulation (TMS) have revealed that corticospinal excitability (CSE) is modulated during preparation for motor action. Changes in CSE may reflect selection and preparation of motor action (*response competition*), prevention of premature responses (*impulse control*), or suppression of task-unrelated afferents to improve the signal-to-noise ratio in the corticospinal representation of prepared action (*noise reduction*). Two experiments were conducted to distinguish between these proposals. Participants completed a variable foreperiod choice reaction time task. TMS was applied at one out of three time-points during the preparatory period. In Experiment 1, participants were provided with information about type and timing of forthcoming action. In Experiment 2, participants were provided with information about the type of impending action whilst we manipulated (low / high) external temporal uncertainty (ETU: temporal uncertainty induced by varying the timing of imperative events). In Experiment 1 and 2, CSE was elevated for prepared versus unprepared action throughout the entire preparatory period. We found relative CSE suppression for the prepared *and* unprepared action shortly before imperative events (Experiment 1) or shortly after warning cues (Experiment 2). Temporal information therefore delays preparatory processes until shortly before action. In Experiment 2, we found that stronger beneficial effects of temporal information on behavioural performance correlate (a) with a larger relative difference in CSE between prepared and unprepared actions and (b) lack of CSE suppression for prepared action before action. The first finding reveals that temporal information affects *response competition*. The latter finding suggests that *impulse control* (and not *noise reduction*) drives CSE suppression for prepared actions.

Key words: Transcranial Magnetic Stimulation (TMS), action preparation, motor preparation, temporal uncertainty, even preparation, temporal preparation, inhibition

Advance information about impending actions improves performance. Reaction times decrease with the amount of information provided about the type of forthcoming motor response (Fitts, 1954; Fitts & Peterson, 1964; Hick, 1952; Hyman, 1953; Schneider & Anderson, 2011), its timing (Bertelson, 1967; Bertelson & Tisseyre, 1968; Klemmer, 1956, 1957; Los, Knol, & Boers, 2001; Niemi & Naatanen, 1981), or both (Bertelson & Boons, 1960; Holender & Bertelson, 1975; Spijkers, 1990; Spijkers & Walter, 1985). In two experiments, we studied how temporal and event uncertainty, that is, limited information about the timing of type of imperative events influence motor preparation, using Transcranial Magnetic Stimulation (TMS).

Changes in corticospinal excitability (CSE) during the preparatory period (i.e. prior to imperative events) suggest that several processes underlie the preparation for imperative events and forthcoming motor responses. First, successful selection, preparation, and execution of actions may be instantiated by an anticipatory relative increase in CSE in the corticospinal representation of the prepared action (*response competition*; Bestmann et al., 2008; Cisek, 2006; Cisek & Kalaska, 2005, 2010; Duque, Lew, Mazzocchio, Olivier, & Ivry, 2010; Michelet, Duncan, & Cisek, 2010; Reynolds & Ashby, 1999). Such response competition may occur by increasing the neural excitability for the prepared action (van Elswijk et al., 2007), decreasing excitability for unprepared alternatives (Julie Duque et al., 2010), or both. Second, during preparation for action, neural excitability for the prepared action may be selectively suppressed to prevent premature responses (*impulse control*; Davranche et al., 2007; Duque & Ivry, 2009; Duque et al., 2010; Sinclair & Hammond, 2008, 2009). Third, an adaptive mechanism may prepare the corticospinal representation of the selected action for receiving and implementing the voluntary motor command by decreasing background noise (i.e. task-unrelated afferents; *noise reduction*; Hasbroucq, Kaneko, Akamatsu, & Possamaï, 1997, 1999; Hasbroucq, Osman, et al., 1999). This would appear as an overall decrease in neural excitability for the prepared action representation.

Impulse control and *noise reduction* are difficult to distinguish because they both predict a decrease in CSE during the preparatory period for the selected and prepared action. However, if CSE suppression for the selected and prepared action is attenuated, *noise reduction* predicts slower motor responses whereas *impulse control* predicts more premature and presumably faster motor responses.

While these three accounts link changes in CSE to preparatory processes in anticipation of imperative events and motor responses, changes in CSE may also reflect processes unrelated to anticipation of imperative events. The warning stimulus, for example, may trigger an immediate but transient increase in CSE for the instructed response (*cue activation*; Boulinguez, Jaffard, Granjon, & Benraiss, 2008). In the face of such a transient increase, subsequent levels of CSE would seem suppressed. Gradual changes in CSE throughout the preparatory period may also reflect processes that underlie keeping track o the passage of time (Janssen & Shadlen, 2005; Mita et al., 2009) rather than motor preparation (*time tracking*). These two alternatives are particularly viable in constant (Hasbroucq et al., 1997; Hasbroucq, Kaneko, et al., 1999; Hasbroucq, Osman, et al., 1999) or variable foreperiod tasks (van Elswijk et al., 2007) when the timing of the TMS is locked to the warning stimulus (i.e. a constant delay between warning stimulus and TMS). Finally, one study has suggested that CSE decreases in anticipation of the TMS pulse to reduce the evoked muscle twitch, in particular when the timing of the TMS is predictable (Takei, Hashimoto, Hagura, Matsumura, & Naito, 2005).

In the current study, we assess the effects of advance information about the timing of imperative events on changes in CSE prior to such events. We conducted two experiments in which participants completed a variable foreperiod task. In Experiment 1, reliable advance information about the timing of imperative events was provided and thus removed any temporal uncertainty. TMS was applied at one out of three possible times-points during the preparatory period, time-locked to the imperative event, to measure changes in CSE. We reasoned that when the timing of the imperative event is known, changes in CSE should largely occur shortly before the imperative event (Carlsen & Mackinnon, 2010), if these changes indeed reflect motor preparation in anticipation of the imperative event. Such an effects would speak against both *cue activation* and *time tracking* as underlying mechanisms for delay-period CSE changes. The former instead predicts changes early during the preparatory period, whereas the latter instead predicts a gradual change across the entire preparatory period. This experiment thus allowed distinguishing between motor and non-motor related explanations of changes in CSE.

In addition we reasoned that there should be a relative increase in CSE for prepared actions, and decrease for unprepared actions, as predicted by *response competition* (Bestmann et al., 2008; Cisek, 2006; Cisek & Kalaska, 2005, 2010; Julie

Duque et al., 2010; Michelet et al., 2010; Reynolds & Ashby, 1999). The increase in CSE for the prepared action, however, may be attenuated or (over-)compensated by *impulse control* or *noise reduction* (Duque & Ivry, 2009; Duque et al., 2010; Hasbroucq, Akamatsu, Burle, Bonnet, & Possamaï, 2000; Hasbroucq et al., 1997, 1997; Hasbroucq, Kaneko, et al., 1999, 1999; Hasbroucq, Osman, et al., 1999).

By contrast, in Experiment 2 we explored changes in CSE under conditions of temporal uncertainty. Participants now did not receive information about the timing of the imperative event and consequently experienced *external temporal uncertainty* (ETU), in addition to constant *internal temporal uncertainty* (ITU), as temporal uncertainty was induced by unpredictably varying the timing of the IS from one trial to the next. Most studies on the neurophysiology of action preparation employed fixed FP tasks (Boulinguez et al., 2008; Burle, Bonnet, Vidal, Possamaï, & Hasbroucq, 2002; Duclos, Schmied, Burle, Burnet, & Rossi-Durand, 2008; Hasbroucq et al., 1997; Hasbroucq, Kaneko, et al., 1999; Hasbroucq, Osman, et al., 1999) but see (van Elswijk et al., 2007). However, preparation under conditions of ETU may differ from preparation under conditions of ITU. Under conditions of ETU, the probability of the imperative stimulus changes throughout the FP, which is referred to as the *hazard function* (Coull, Cheng, & Meck, 2011; Nobre, Correa, & Coull, 2007). Typically, if the imperative event has not yet occurred, then it is increasingly likely to occur soon. For a Gaussian distribution, for example, the probability of the imperative event (i.e. posterior probability or hazard rate) increases monotonically throughout the entire FP. In Experiment 2, we therefore asked whether CSE reflects anticipation of increasing hazard rate either by a gradually developing relative difference in CSE for prepared versus unprepared action (*response competition*) or by an increasing suppression of CSE for prepared action only (*impulse control / noise reduction*).

Methods

Experiment 1: changes in corticospinal excitability (CSE) during preparation for imperative events in the absence of temporal uncertainty

Experiment 1 was conducted to investigate the neurophysiological correlate of action preparation when both temporal and event uncertainty were removed by advanced information. Participants completed a variable foreperiod (FP) choice reaction time task. Throughout the entire FP, an analogue clock provided participants with continuous, accurate, and reliable information about the timing of the imperative stimulus (IS). This removed both ETU and ITU. Participants also received reliable advance information about the type of required action at the start of each trial. Participants were thus fully informed about *what* to do, and *when* to do it. TMS was given at one out of three time-points during the FP, with the timing of TMS being locked to the timing of the imperative stimulus (Figure 4.1).

We expected participants to respond shortly after the IS given that they fully knew *what* to do, and *when* to do it, thus removing the necessity for *time tracking*. Neither reaction times nor CSE should be affected by variability in foreperiod duration for the same reason. Instead, we expected that CSE relates to the anticipation of imperative events and motor responses, and that changes in CSE should therefore occur just before the imperative event, but not early on during the FP (contrary to the predictions of *cue activation* or *time tracking*). The direction of change in the selected and prepared versus unprepared action will allow us to distinguish between *response competition*, *impulse control*, and *noise reduction*.

Experiment 2: changes in corticospinal excitability (CSE) during preparation for imperative events under conditions of temporal uncertainty

In Experiment 1, we removed temporal uncertainty to distinguish between motor (*response competition*, *impulse control*, *noise reduction*) and non-motor (*cue activation*, *time tracking*) explanations of changes in CSE prior to the IS. In Experiment 2, we reintroduced ETU to distinguish between different motor-related explanations of changes in CSE. Specifically, we tested whether changes in CSE reflect participants' anticipation of a change in the hazard rate of the IS. The timing of the TMS was chosen carefully to explore these effects of hazard rate on CSE. The level of ETU determined the probability density function of the IS (by setting the standard deviation), and consequently the cumulative probability of the IS (Figure 4.1C), and the conditional probability of the IS or hazard rate (Figure 4.1D) over time. For high ETU, the increase in cumulative probability of the IS is more gradual with an earlier onset (Figure 4.1C). The hazard rate thus increases gradually with a relatively shallow slope (Figure 4.1D) for high compared to low ETU. TMS timing was chosen to probe changes in CSE at different levels of cumulative IS probability / hazard rate.

Based on previous studies and Experiment 1, we expected to find an increase in CSE for the selected and prepared action, which would support *response competition.* Further, we expected a decrease in CSE for the unprepared action alternative throughout the FP*.* This would increase the relative difference in CSE between selected versus unselected action alternatives and support *response competition*. And finally, we expected a decrease in CSE for the prepared versus unprepared actions throughout the FP that reflects either *impulse control* or *noise reduction*. In Experiment 1, the increase in CSE was not modulated over time, and we therefore we did not expect to find a modulation of this increase by the hazard function. However, we expected to find a modulation of the decrease in CSE by the hazard function in both the prepared and the unprepared muscle. In particular, for low compared to high ETU, we expected a strong decrease in CSE shortly before the IS, reflecting anticipation of the strong increase in hazard rate.

Participants

16 participants took part in Experiment 1 (mean age = 22.9 years, min. = 19, max. = 28; all right-handed; 7 female), and 15 participants took part in Experiment 2 (mean age = 23.5 years, range: 20-31 years; one left-handed, eight female). All participants had corrected or corrected-to-normal vision. They received £20 remuneration. Before participation, written informed consent was obtained. This study was approved by a local ethics committee in line with the declaration of Helsinki.

Procedure and design

Experiment 1: changes in corticospinal excitability (CSE) during preparation for imperative events in the absence of temporal uncertainty

Participants sat comfortably in front of a computer screen at approximately 70 cm viewing distance, with their right index and little finger resting on the left and right buttons respectively of a custom-made button box. Their hands were placed so that they could comfortably press the buttons without any pre-contraction of the target muscle during the preparatory period. A comfortable chair as well as arm support further ensured that participants could maintain relaxation in the target muscles throughout the experiment. Stimuli were presented using Matlab and the Cogent2000 toolbox (University College London, http://www.vislab.ucl.ac.uk/ Cogent2000/index.html).

Participants completed a variant of the variable FP choice reaction time task. Trial onset was signalled by a white fixation cross, appearing at the centre of the screen on black background. This was followed, after 200ms, by a simple analogue clock face (a white circle with a black clock hand; see Figure 4.1), superimposed on a red square, presented at central fixation. The red square instructed participants to prepare their action: it served as the warning stimulus (WS). Two arrows pointing both either towards the left or right were placed above and below the clock. Left-hand arrows instructed an index finger response (90% of all trials), right-hand arrows instructed a response with the little finger. At trial onset, the clock hand was in the 12 o'clock position. It completed one full rotation on each trial at constant speed. The clock speed varied across trials to accommodate different FP duration. When the clock hand returned to the 12 o'clock position, the colour of the square changed from red to green. Participants were instructed to respond as fast as possible to the change in colour, which thereby served as the IS. The clock allowed participants to predict the timing of the colour change with high accuracy.

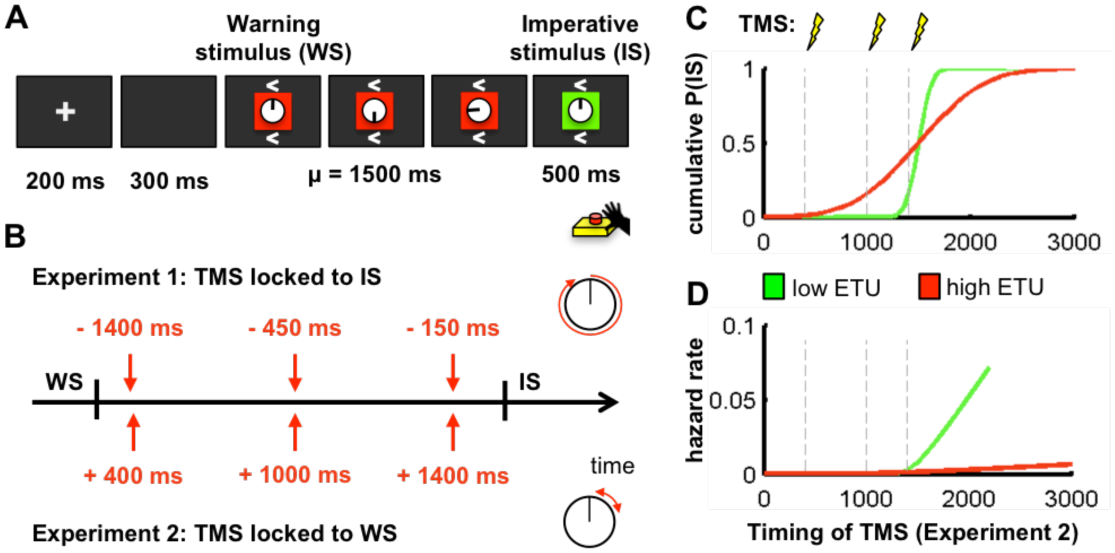


Figure 4.1: Experimental design. A. Participants completed a variable foreperiod simple reaction time task. Trial onset was signalled by appearance of a fixation cross, followed by the onset of a clock superimposed on a red square. Arrows above and below the clock instructed participants to prepare a right index (left arrows: 90 % of all trials) or right little finger button press (right arrows: 10 % of all trials). **B.** In Experiment 1, the clock completed one full rotation on each trial. Once it returned to the 12 o'clock position, the colour of the square changed to green which prompted participants to respond. In Experiment 2, the clock hand moved in a random walk until IS appearance. In Experiment 1, TMS was applied either 150ms, 450ms or 1400ms before the imperative stimulus (IS). In Experiment 2, TMS was applied 400ms, 1000ms, or 1400ms after the warning stimulus (WS). **C.** Foreperiods (FP) were sampled from a Gaussian distribution with a mean of 1500ms and a standard deviation of either 100 (low FP duration variability / ETU) or 500 (high FP duration variability / ETU). For high compared to low FP duration variability / ETU, the cumulative probability of IS occurrence increased more gradually with an earlier onset. **D.** While there was a steep increase in hazard rate for low FP duration variability / ETU, starting at around 1400ms, the hazard rate developed more gradually for high ETU. In Experiment 2, the timing of TMS was chosen based on the cumulative probability of the occurrence of the IS and hazard rate (for more information, see text).

FP durations were sampled from truncated Gaussian distributions. The mean was set at 1500ms. The Gaussians were truncated at 500ms and 2500ms (Hackley, 2009). FP variability was manipulated by varying the standard deviation (SD = 100 / 500) across blocks. Participants completed six blocks of 60 trials each. FP variability was blocked, with three consecutive blocks of either high or low FP variability, respectively. The order of FP variability was counterbalanced across participants. Participants received feedback about their average reaction time every 15 trials to encourage preparation and quick responses to the IS.

Experiment 2: changes in corticospinal excitability (CSE) during preparation for imperative events under conditions of temporal uncertainty

Procedures and design were identical to Experiment 1 with one important exception: in the Experiment 2, the movement of the visual clock was uninformative about the time of occurrence of the IS. The clock hand started in the 6 o'clock position at trial onset and moved back and forth in a random fashion, at constant speed. Consequently, participants experienced ETU, due to variability in FP duration, as well as ITU, due to limited accuracy in time estimation. Despite being uninformative, the moving clock was included to match the stimulus features of Experiment 1.

Electromyographic recordings (EMG)

Surface EMG was recorded from the right first dorsal interosseous (rFDI; index finger flexion), and the right abductor digiti minimi (rADM; little finger flexion). EMG was recorded with Ag/AgCl disc electrodes in a tendon-belly montage, amplified (gain: 1000), band-pass filtered (10Hz – 1 kHz), digitised (5kHz), and stored on a laboratory computer for later off-line analysis. During the experiment, EMG was monitored and the experimenter instructed participants to relax whenever necessary.

Transcranial Magnetic Stimulation (TMS)

TMS was delivered through a 70 mm figure-of-eight coil connected to a monophasic Magstim 200 magnetic stimulator (Magstim, Whitland, Dyfed, UK). The coil was placed flat on the scalp over the left motor cortex (lM1) with the handle pointing backward and laterally at 45° angle away from the midline. Thus, the current induced in the neural tissue was directed approximately perpendicular to the line of the central sulcus and therefore optimal for activating the corticospinal pathways trans-synaptically (Brasil-Neto et al., 1992).

The stimulator coil was initially moved over the left hemisphere, with a fixed slightly supra-threshold intensity, to determine the optimal position for eliciting MEPs in the rFDI. The optimal position was then marked on the scalp to ensure optimal coil placement throughout the experiment. Subsequently, 1mV motor threshold (MT_{1mV}) was determined to the nearest 1% stimulator output, and defined as the lowest stimulator output required to produce MEPs of 1mV peak-to-peak amplitude in the rFDI (mean = 48.1%, range = 32% – 62%). Furthermore, we ensured that with this procedure, MEPs were also reliably evoked in the rADM. Later normalisation accounted for activity differences at baseline.

Experiment 1: changes in corticospinal excitability (CSE) during preparation for imperative events in the absence of temporal uncertainty

A single TMS pulse was applied on 50% of trials, either 1050ms, 450ms, or 150ms before the IS, with equal probability for each time-point. Consequently, the time interval between the WS and the TMS was variable due to variability in FPs. On the remaining 50% of all trials, no TMS was applied. This ensured that participants could not use the TMS pulse instead of the WS as a temporal cue for action preparation. It also reduced predictability of the timing of the TMS. In addition, 15 TMS pulses were delivered while the participant was at rest before and after each block. Participants were instructed to relax and fixate at the centre of the screen, with their right index and little finger resting on the response buttons, during the entire experiment and during baseline.

Experiment 2: changes in corticospinal excitability (CSE) during preparation for imperative events under conditions of temporal uncertainty

TMS location and intensities were determined as above (mean TMS: 49.7%, range = 34% – 66%). Contrary to the first experiment, the timing of the TMS was locked to the WS: participants now had to rely on the WS as an anchor point for temporal preparation. TMS was given on 50% of all trials 400ms, 1000ms, or 1400ms after the WS, with equal probability for each time point. On the remaining 50% of trials, no TMS was applied. These times for TMS were chosen with respect to the truncated Gaussians (see Figure 4.1CD) from which FPs were sampled. For the early stimulation time (400ms), both the cumulative probability of the IS and the hazard rate were zero for both high and low ETU as Gaussians were truncated at 500ms. As such, it served as a reference because we assumed that preparation should be minimal at this time-point, irrespective of whether FP duration was overall more variable or not. For the intermediate TMS time point (1000ms), the cumulative probability of IS occurrence was close to zero for low ETU condition, but increased to 15.9% for the late TMS time-point (1400ms). Hazard rate increased by 0.00029 from close to zero (< 0.0001) to 0.0029 and was bound to increase shortly after late TMS (Figure 4.1D). By contrast, for the high ETU, the IS was likely to occur before the intermediate TMS time-point on 15.9% of all trials and this probability increased to 42.1% for the late TMS time-point. Thus, by the time participants received late TMS, they had already experience the IS at an earlier time on 42.1% of all preceding trials. The hazard rate increased from by 0.0007 from 0.0005 to 0.0014 and was bound to increase comparatively slowly thereafter. Put simply, while keeping the absolute time of TMS fixed with respect to the WS, the cumulative probability of IS occurrence and the hazard rate significantly varied between the low and high FP variability condition, respectively.

Data analyses

We excluded all trials with premature responses (reaction times < 0ms), incorrect behavioural responses (e.g. a response with the little finger when instructed to respond with the index finger), and response omissions from further analysis. In addition, we excluded all trials on which participants were prompted to respond with the little finger (10% of all trials). These trials served to encourage participants to pay attention to the WS. Outliers in reaction times of the remaining trials were identified and excluded using Grubb's test. To test for differences in reaction times, we computed a 2 x 4 within-subjects repeated measures ANOVA on mean reaction times with FP variability (low, high) and TMS (none, early: -1400ms, intermediate: -450ms, late: -150ms) as factors.

For trials with TMS, we extracted MEP peak-to-peak amplitudes as well as pre-TMS EMG activity from the EMG traces recorded from rFDI and rADM. All trials with a MEP amplitude below 0.1 mV were excluded from further analysis (Mars et al., 2007). As pre-TMS EMG activity is known to affect MEP size, we excluded all trials with a root mean square of pre-TMS EMG activity exceeding 0.075 measured over a time window 100ms prior to the TMS pulse (Mars et al., 2007). Then, to ensure that pre-TMS EMG activity was similar across all conditions, we ran a Grubb's test on the root mean square of pre-TMS EMG activity on all trials for each subject separately to determine and exclude any outliers in pre-TMS EMG activity. Similarly, Grubb's test was used to identify and exclude outliers in MEPs for each experimental condition and participant separately.

Similarly, MEP peak-to-peak amplitudes were extracted from the baseline data recorded during rest before and after each block. Traces were excluded if MEP amplitude was smaller than 0.1mV and if pre-EMG activity exceeded 0.075, see above. Outliers in pre-EMG activity were identified and excluded using Grubb's tests. MEP amplitudes recorded during one experimental block were divided by the mean baseline MEP amplitude recorded before and after the same block, separately for each muscle. This normalisation procedure accounts for differences in MEP amplitude, e.g. due to coil displacement or fatigue, and allows for meaningful comparison between MEPs recorded in the rFDI and the rADM.

To test for condition specific differences in MEP amplitude, a 2 x 3 x 2 within-subjects repeated measures ANOVA was computed on mean MEP amplitude, averaged across all remaining trials, with FP variability (low, high), TMS time (early: -1400ms, intermediate: -450ms, late: -150ms), and muscle (prepared, unprepared) as factors. As participants were prompted to respond with their index finger on all trials included in this analysis, rFDI was the prepared and rADM the unprepared muscle. Finally, we tested for increase, or decrease, in normalised MEP amplitude compared to baseline using one-sample t-tests. For all tests, we adopted a significance threshold of $\alpha=0.05$.

Results

Experiment 1: changes in corticospinal excitability (CSE) during preparation for imperative events in the absence of temporal uncertainty

Two participants were excluded because their error rates exceeded 25% of all trials. Of the remaining participants, we excluded 10.1% of all trials due to premature responses (8.8% of all trials), response omissions (0.8%) and incorrect button presses (0.5%). An additional 6.3% of all trials were excluded due to small MEP amplitude or pre-TMS EMG activity.

The 2 x 4 ANOVA on mean reaction times revealed a significant effect of TMS only ($F_{(3,42)} = 23.91$, $p < 0.001$, $\eta_p^2 = 0.631$). Participants responded significantly slower if no TMS was given (mean = 143.1ms, SE = 14.0) compared to early (mean = 116.6ms, SE = 10.7; $t_{(14)} = 3.95$, $p = 0.005$), intermediate (mean = 89.1ms, SE = 7.2; $t_{(14)} = 5.71$, $p < 0.001$), and late TMS (mean = 103.0ms, SE = 10.5; $t_{(14)} = 6.45$, $p < 0.001$, see Figure 4.2).

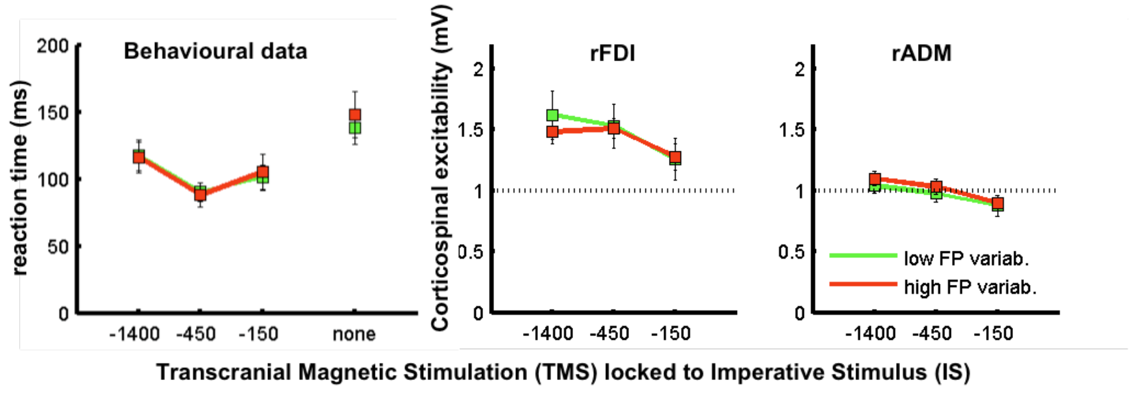


Figure 4.2: Reaction times and changes in corticospinal excitability (CSE) under conditions of full removal of temporal uncertainty. Participants responded shortly after occurrence of the imperative stimulus (IS). The absence of a difference between low versus high foreperiod (FP) variability shows that participants used the explicit information about the timing of IS occurrence for preparation of actions. Participants responded faster on trials with versus no TMS. Corticospinal excitability (as reflected in mean MEP amplitudes) was higher in the selected and prepared (right first dorsal interosseous; rFDI) versus unprepared muscle (right abductor digiti minimi; rADM), and decreased towards the end of the foreperiod. This decrease was more pronounced in the prepared relative to the unprepared muscle.

The 2 x 3 x 2 ANOVA on mean MEP amplitude revealed an increase in MEP amplitude in the prepared compared to the unprepared muscle ($F_{(1,14)} = 13.87$, $p = 0.002$, $\eta_p^2 = 0.498$). TMS time was also significant ($F_{(2,28)} = 22.43$, $p < 0.001$, $\eta_p^2 = 0.616$), due to a decrease in MEP amplitude for late compared to intermediate TMS ($t_{(14)} = 4.82$, $p < 0.001$) while there here was no difference in MEPs for early versus intermediate TMS ($p > 0.01$). Finally, the ANOVA revealed a marginally significant interaction between muscle and TMS time ($F_{(2,28)} = 3.09$, $p = 0.062$, $\eta_p^2 = 0.181$). Two 3 x 1 repeated measures ANOVAs on mean MEPs with the factor TMS time, collapsed across FP variability and computed separately for the prepared and unprepared muscle, revealed significant effects of TMS time on MEP amplitudes for both muscles (prepared: $F_{(2,28)} = 16.95$, $p < 0.001$; unprepared $F_{(2,28)} = 12.76$, $p < 0.001$). Paired-sample follow-up t-tests show that, in the prepared muscle MEP amplitude decreased for late versus intermediate TMS ($t_{(14)} = 4.54$, $p < 0.001$) but not for intermediate versus early TMS ($p > 0.1$). Similarly, MEPs decreased for late versus intermediate TMS ($t_{(14)} = 4.02$, $p = 0.002$) but not for intermediate versus early TMS ($p > 0.1$) in the unprepared muscle. Thus, the marginally significant interaction between muscle and TMS time was driven by a stronger decrease in the prepared muscle for late compared to intermediate TMS (see Figure 4.2).

Mean normalised MEP amplitude, collapsed across the non-significant factor FP variability, increased above baseline in the prepared muscle only for early ($t_{(14)} = 4.11$, $p = 0.001$) and intermediate TMS time ($t_{(14)} = 4.39$, $p < 0.001$). No further comparisons were significant ($p > 0.1$).

Experiment 2: changes in corticospinal excitability (CSE) during preparation for imperative events under conditions of temporal uncertainty

One participant was excluded because the percentage of behavioural errors exceeded 25% of all trials. Of the remaining participants, 7.3% of all trials were excluded due to behavioural error, 4.9% of which due to premature responses. An additional 7.3% of all trials were excluded due to small MEP amplitude or pre-TMS EMG activity.

The 2 x 4 ANOVA on mean reaction times revealed a significant effect of ETU ($F_{(1,13)} = 12.22$, $p = 0.003$, $\eta_p^2 = 0.449$). Participants responded faster for low (mean = 264.67ms, SE = 7.83) compared to high ETU (mean = 276.01ms, SE = 6.92). In addition, TMS time was significant ($F_{(3,39)} = 26.70$, $p < 0.001$, $\eta_p^2 = 0.640$). Participants responded slower when no TMS was given (mean = 297.7ms, SE= 10.6) compared to early (mean = 265.9ms, SE = 7.0; $t_{(13)} = 4.41$, $p < 0.001$), intermediate (mean = 258.2ms, SE = 6.8; $t_{(13)} = 5.82$, $p < 0.001$), and late TMS (mean = 259.6ms, SE = 7.53; $t_{(13)} = 6.03$, $p < 0.001$).

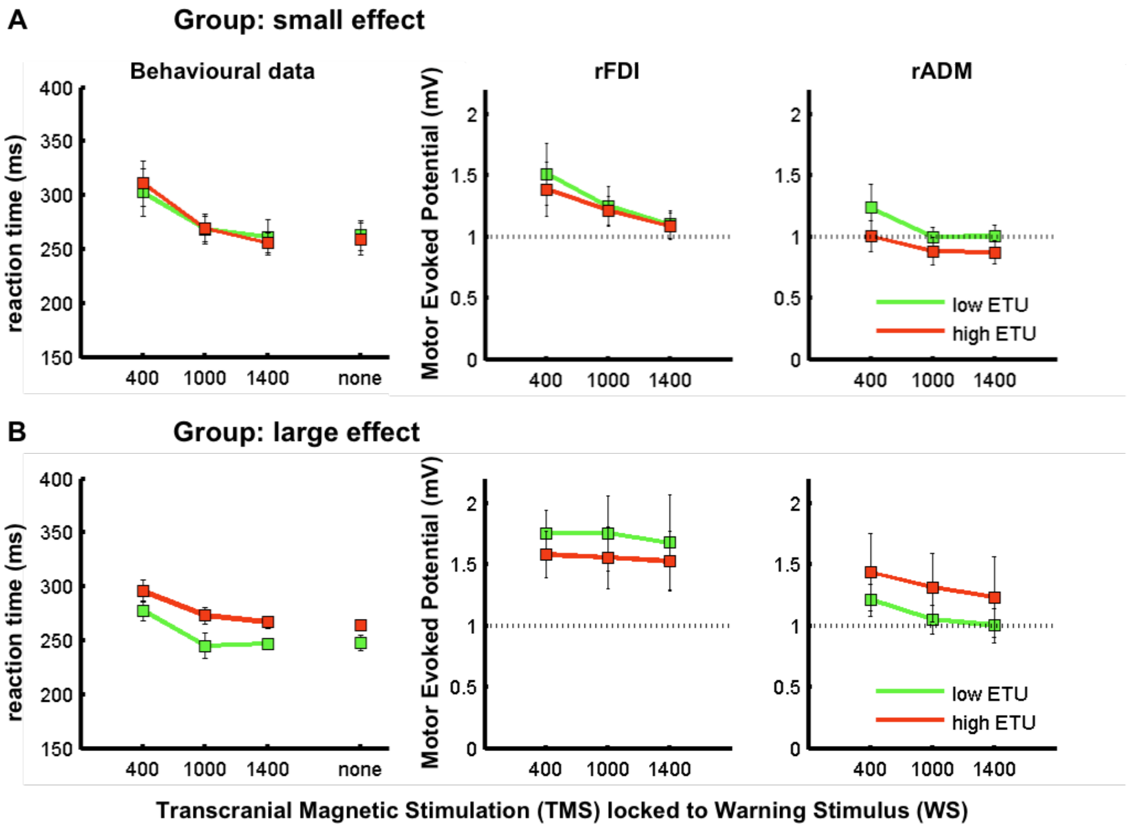


Figure 4.3: Reaction times and changes in corticospinal excitability (CSE) under conditions of external temporal uncertainty (ETU). Reaction times under condition of high external temporal uncertainty (ETU) were subtracted from reaction times under conditions of low ETU. A negative difference in reaction time thus reveals a benefit of advance information provided by the WS about the timing of the IS on action preparation. We then performed a median-split to sub-divide participants into two groups (small / large effect group) according to their difference in reaction time for high versus low ETU. Differences in reaction times were due to an improvement in performance when ETU was low compared to high. This difference was pronounced and absent in the large and small effect group, respectively. Averaged across groups, CSE increased for the selected and prepared (right first dorsal interosseous; rFDI) compared to the unprepared action (right abductor digiti minimi; rADM). Further, CSE decreased early on during the preparatory period (early / 400ms vs. intermediate / 1000ms) while it remained stable for the remainder (intermediate / 1000ms vs. late / 1400ms). The effect of ETU on CSE for the selected compared to the unselected action differed for the two groups. When ETU was low, the difference in CSE between the prepared and unprepared action was pronounced in the large effect group. Similarly, the effect of time on the selected compared to the unselected action differed between groups. There was a stronger decrease over time in CSE for the prepared action in the group with the small behavioural effect.

The 2 x 3 x 2 ANOVA on normalised mean MEP amplitude revealed an increase in MEPs in the prepared versus the unprepared muscle ($F_{(1,13)} = 14.92$, $p = 0.002$, $\eta_p^2 = 0.534$). In addition, the ANOVA revealed a significant effect of TMS time ($F_{(2,26)} = 6.07$, $p = 0.007$, $\eta_p^2 = 0.318$). MEP amplitude decreased for intermediate versus early TMS ($t_{(13)} = 2.59$, $p = 0.022$) while there was no further decrease for late relative to intermediate TMS ($t_{(13)}$ = 1.38, p = 0.190). No other effects were significant. In particular, there was no significant effect of ETU (all p > 0.1).

Comparison of normalised MEP amplitude, collapsed across the non-significant factor ETU, revealed an increase above baseline in the prepared muscle for early TMS only ($t_{(13)}$ = 3.90, p = 0.002). No other comparison against baseline was significant (p > 0.01).

The lack of an effect of ETU on MEPs was surprising given the significant effect of ETU on reaction times. This may be due to the high inter-subject variability in behavioural performance, which may determine how ETU affects MEPs, and may cancel out on average. To test for this possibility, we sought to relate the size of the behavioural effect to changes in MEP amplitude. Put differently, we aimed to explore whether the benefit of having better advance information about the timing of the imperative event under conditions of low ETU is reflected in changes in MEPs. To this end, we first determined the size of the behavioural effect for each participant by subtracting reaction times for high ETU from reaction times for low ETU (here, collapsed across all trials with or without TMS). This subtraction revealed the degree to which participants were able to benefit from warning cues that were more informative about the timing of the imperative stimulus under conditions of low versus ETU. We then performed a median-split and divided participants in two groups based on whether their difference score was higher (i.e. small benefit of more informative warning cue) or lower (i.e. large benefit of more informative warning cue) than the median difference score. To determine the effect of ETU on MEPs, we then re-analysed the MEP data with a 2 x 3 x 2 x 2 mixed ANOVA with ETU, TMS time, and muscle as within-subjects factors, and group (small, large behavioural effect) as a between-subjects factor.

As expected given the previous analysis, the 2 x 3 x 2 x 2 mixed ANOVA revealed higher MEPs in the prepared muscle ($F_{(1,12)}$ = 14.89, p = 0.002, η_p^2 =

0.554), and a decrease in MEPs over time ($F_{(2,24)} = 5.96$, $p = 0.008$, $\eta_p^2 = 0.332$). Importantly, the analysis also revealed a significant interaction between muscle, ETU, and group ($F_{(1,12)} = 4.77$, $p = 0.050$, $\eta_p^2 = 0.284$).

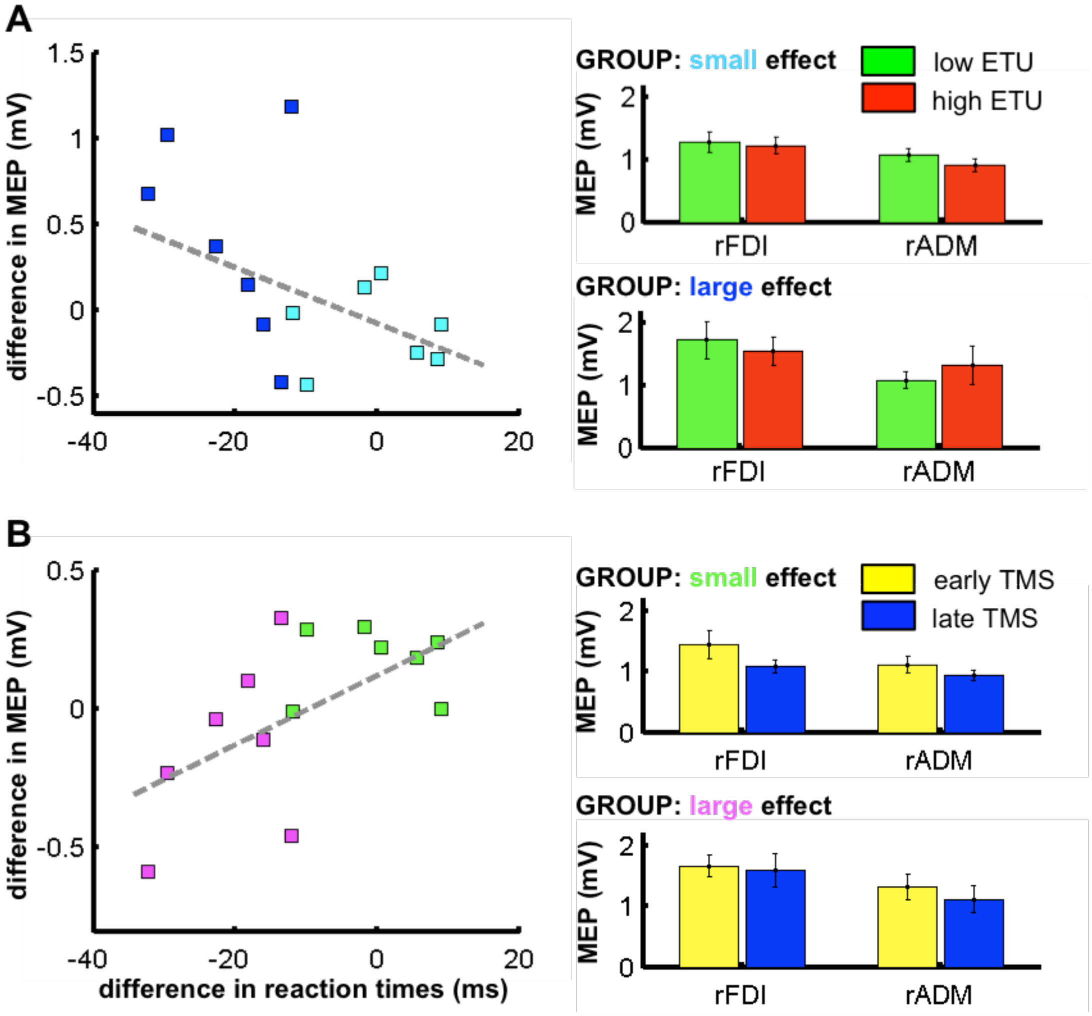


Figure 4.4: Correlation between behavioural performance and corticospinal excitability (CSE) in the prepared and unprepared muscle. Reaction times under conditions of high *external temporal uncertainty* (ETU) were subtracted from reaction times under conditions of low ETU. Negative difference scores thus reflect an improvement in reaction times for low ETU when the warning cue was more informative about the timing of the imperative stimulus. **A.** The left panel shows the relation between the difference in reaction time (low – high ETU: x-axis of scatter plot) and the modulation of CSE for the prepared versus unprepared action under conditions of low versus high ETU. The difference in reaction time correlated with a selective increase in CSE under conditions of low ETU for the prepared versus unprepared action, relative to the difference in CSE between prepared versus unprepared action at high ETU. Thus, the difference in CSE for the prepared versus unprepared action increased as participants benefitted more from the WS when it was more informative about the timing of the IS under conditions of low versus high ETU. **B.** The left panel shows the relation between the difference in reaction time (low – high ETU: x-axis of scatter plot) and the modulation of CSE during the preparatory period for the prepared and unprepared action. The decrease in CSE for the prepared action diminished with increasing size of the behavioural effect. Changes in CSE over time thus decreased as participants benefitted more from the information provided by the WS about the timing of the IS.

We further analysed this interaction by relating the difference underlying this significant 3-way interaction effect to the single-subject behavioural effect, rather than using a median-split approach as in the previous analysis. To this end, we first collapsed across the non-significant factor time and then computed the difference between the prepared and the unprepared muscle for both high and low ETU. Then, we subtracted these two difference scores from each other (i.e. a significant 3-way interaction in an ANOVA suggests a significant difference in difference scores) before correlating this resulting “difference in difference scores” to the single-subject behavioural effect. The correlation was negative and significant ($r_{(14)}$ = -0.553, p = 0.0401; see Figure 4.4). As shown in Figure 4.4, the correlation was driven by a larger relative increase in CSE in the selected and prepared versus unprepared muscle in participants that were able to benefit from low levels of ETU (i.e. large effect group), but only under conditions of low ETU.

We also found a 3-way interaction between muscle, time, and group ($F_{(2,24)}$ = 3.45, p = 0.048, η_p^2 = 0.223). Following the same logic as above, we collapsed across the non-significant factor ETU, and computed the difference between late and early TMS time points for the unprepared muscle. This difference score was then subtracted from the difference between late and early TMS in the prepared muscle. The correlation between the resulting “difference in difference scores” and the single-subject behavioural effect was positive and significant ($r_{(14)}$ = 611, p = 0.020). It was driven primarily by a smaller reduction in MEP size in the prepared muscle for late versus early TMS when participants were able to benefit from low levels of ETU (i.e. large effect group). When participants did not use the information about the timing of the imperative stimulus provided by the warning cue, or used it to a lesser extent, the decrease in MEPs in the prepared muscle over time was comparatively large.

Finally, to determine whether behavioural responses were driven by an improvement in performance for low ETU or a worsening for high ETU, we reanalysed the reaction times per group, using a 2 x 4 x 2 mixed ANOVA. This analysis revealed a significant interaction between ETU and group ($F_{(1,12)} = 22.47$, $p < 0.001$, $\eta_p^2 = 0.652$) in addition to a significant main effect of ETU ($F_{(1,12)} = 22.33$, $p < 0.001$, $\eta_p^2 = 0.650$) and TMS time ($F_{(3,36)} = 24.22$, $p < 0.001$, $\eta_p^2 = 0.669$). The interaction between ETU and group was caused by a significant decrease in reaction times for low ETU (mean = 254.4ms, SE = 12.19) versus high ETU (mean = 275.1ms, SE = 10.72) in the high effect group ($t_{(6)} = -6.95$, $p < 0.001$) while there was no difference in the low effect group between low ETU (mean = 273.9ms, SE = 12.19) and high ETU (mean = 273.9ms, SE = 10.72; $t_{(6)} = 0.01$, $p = 0.992$). Participants thus benefited from warning cues that were more informative about the timing of the imperative stimulus under conditions of low versus high ETU in the high effect group. Reaction times under conditions of high ETU were comparable across groups. No further effects were significant (all $p > 0.1$). As the effect of TMS did not interact with group, it was not further explored.

Discussion

In Experiment 1, we sought to distinguish between motor (*competition resolution*, *impulse control*, *noise reduction*) and non-motor (*cue activation*, *time tracking*) explanations of CSE changes prior to imperative events. Additionally, we aimed to find evidence for one (or more) of the three motor-related explanations of CSE changes. To this end, we investigated the development of CSE during the preparatory period when participants were provided with full information about the timing of the forthcoming imperative event (removing the necessity of *time tracking*) and the type of required motor response. Experiment 2 aimed at distinguishing between the three competing motor-related explanations of CSE changes, in particular by assessing whether modulation of CSE by the hazard function can be explained best by *response competition*, *impulse control*, or *noise reduction*.

Experiment 1: changes in corticospinal excitability (CSE) during preparation for imperative events in the absence of temporal uncertainty

Under conditions of complete information about the timing and type of imperative events, participants respond quickly to these events, and differences in foreperiod variability do not impact on reaction times. This shows that participants were able to accurately use both the information provided about the passage of time and the timing of the IS. As this information unambiguously removed all temporal uncertainty (ETU and ITU), any changes in CSE must be independent from processes required for dealing with either temporal or event uncertainty.

The relative increase in CSE observed in the prepared muscle supports the idea that action selection and preparation is implemented by a relative increase in the corticospinal representation of the selected and prepared action, in line with the *response competition* account. Our findings are thus consistent with previous studies that have reported such CSE increase during action preparation (Mars et al., 2007; van Elswijk et al., 2007), and furthermore that such changes reflect the prior expectation about the forthcoming action (Bestmann et al., 2008). In the present experiment, the increase in CSE for the prepared action appeared to be sustained throughout the entire foreperiod. This may suggest that *response competition*, at least the boost in CSE for the selected action, is initiated as soon as information about which action to select and prepare for is provided (in the current experiment, at trial onset) and that the relative differences among competing action representations can be maintained until the response is required.

At the same time, CSE decreased shortly before the IS for both the prepared and unprepared action, suggesting that the preparation-specific increase in CSE occurred in the face of a broader non-specific CSE suppression. The decrease in the prepared muscle may reflect either *impulse control* or *noise reduction* (Davranche et al., 2007; Duque & Ivry, 2009; Duque et al., 2010; Hasbroucq et al., 1997; Hasbroucq, Osman, et al., 1999; Sinclair & Hammond, 2008, 2009; for further discussion, see below) while the decrease in the unprepared muscle may reflect on-going *response competition* (Julie Duque et al., 2010). In other words, under conditions of complete removal of temporal uncertainty, increases in CSE that ensure successful selection and execution of the *selected* action can be initiated as soon as information is provided and sustained throughout the foreperiod. By contrast, in such conditions suppression of the corticospinal representation of the non-selected alternative may be strongest shortly before the anticipated execution of an action. These results complement and extent recent work about the influence of temporal uncertainty on motor preparation (Carlsen & Mackinnon, 2010). These authors showed that accurate and reliable information about the timing of IS occurrence delays motor preparation until approximately 500 ms prior to the response (Carlsen & Mackinnon, 2010). The time course of the present CSE decreases is compatible with this observation, occurring approximately 450-150ms prior to the presentation of the IS. We suggest, in agreement with Carlsen and Mackinnon, that this late decrease in CSE, when temporal uncertainty was fully removed, may be energetically efficient: preparatory processes underlying the CSE decrease are initiated only shortly before the imperative event.

While the decrease in CSE in the unselected and unprepared action can be explained by *response competition*, the concomitant CSE suppression for the selected and prepared action may result from either *impulse control* (Davranche et al., 2007; Julie Duque & Ivry, 2009; Julie Duque et al., 2010; Sinclair & Hammond, 2008, 2009) or *noise reduction* (Hasbroucq, Kaneko, et al., 1999, 1999; Hasbroucq, Osman, et al., 1999). The current data do not allow for distinguishing between these two alternatives. However, our data do clearly show that there must be two inhibitory processes co-occurring during preparation for action: *response competition*, which explains suppression of the unselected action alternative, and either *impulse control* or *noise reduction*, which explain the suppression in CSE for the selected alternative. Our data therefore corroborate recent evidence that *response competition* and *impulse control* may occur concurrently during preparation (Julie Duque et al., 2010). As in the current study, MEPs were suppressed both in the prepared and unprepared muscle, whereas H-reflex amplitudes were attenuated only in the prepared muscles. The authors concluded that *impulse control* targets prepared muscles only and is manifest at the spinal level (see also Prut & Fetz, 1999), whereas suppression of CSE in the unprepared muscle reflects a different inhibitory process, presumably related to *response competition,* being expressed mainly at the cortical level (Julie Duque et al., 2010).

Finally, the decrease in CSE starting just before the anticipated imperative event when temporal uncertainty was fully removed provides evidence against the *cue activation* account (Boulinguez et al., 2008) which would predict a de- or increase in CSE early on during the preparatory period. For the same reason, it appears unlikely that in the current experiment these changes in CSE reflect *time tracking* (Janssen & Shadlen, 2005; Mita et al., 2009) which would predict a gradual de- or increase in CSE over the course of the entire foreperiod. Finally, because TMS was given only on 50% of trials, and time intervals between the WS and TMS were variable, the current results are unlikely to reflect reduction in CSE due to anticipation of TMS pulses (Takei et al., 2005). We conclude that motor accounts of CSE changes best explain our findings.

With regard to the reaction time data, several studies have reported a decrease in reaction times when single TMS pulses are delivered prior to an imperative stimulus (Hasbroucq, Kaneko, et al., 1999). This facilitatory effect of TMS is likely due to cross-modal facilitation (Arieh & Marks, 2008; Baier, Kleinschmidt, & Müller, 2006). TMS causes 'click' sounds that can act as additional sensory cues. Alternatively, single-pulse TMS may affect neural processing in M1 directly, consequently speeding up motor responses. For example, previous work has shown that TMS to M1 can increase reaction times, albeit at subthreshold intensities (Hashimoto, Inaba, Matsumura, & Naito, 2004). Whatever the underlying causes for this observation, in our experiments it had no impact on how participants prepared for action.

Taken together, we show some of the physiological underpinnings of the multiple processes supporting action preparation. *Response competition* ensures the activation of corticospinal representations of prepared actions relative to unprepared alternatives. By contrast, inhibition that specifically acts on the corticospinal representation of the prepared action serves either to prevent premature responses (*impulse control*) or to prepare the cortex for the voluntary motor command (*noise reduction*). CSE suppression for the prepared action shortly before the imperative event reflects on-going *response competition*, now implemented by selectively suppressing the non-selected alternative. The contribution of Experiment 1 is to have isolated these processes, and allowed us to exclude alternative accounts that explain changes in CSE during the preparatory period as being unrelated to anticipation of the imperative event and ensuing motor responses (*cue activation* and *time tracking*).

Experiment 2: changes in corticospinal excitability (CSE) during preparation for imperative events under conditions of temporal uncertainty

In Experiment 1, we removed temporal uncertainty to distinguish between motor (*response competition*, *impulse control*, *noise reduction*) and non-motor (*cue activation*, *time tracking*) related explanations of CSE changes prior to the IS. In Experiment 2, we introduced ETU to distinguish between different motor-related explanations of changes in CSE. Specifically, we tested whether in- or decreases in CSE relate to the hazard function. As expected, participants overall responded faster under conditions of low versus high ETU. This shows that they benefitted from the WS when it was more informative about the timing of the imperative event under conditions of low versus high ETU. However, we observed considerable inter-individual variability in participants' ability to extract temporal information from the WS as a cue for preparation.

Similar to Experiment 1, the relative increase in CSE in the prepared versus unprepared muscle supports the idea that changes in CSE prior to imperative events reflect *response competition* (Bestmann et al., 2008; Cisek, 2006, 2007; Cisek & Kalaska, 2005; Duque et al., 2010; Michelet et al., 2010; Reynolds & Ashby, 1999). Interestingly, the difference in reaction times between low versus high ETU correlates with the relative increase in CSE in the prepared muscle, and the relative decrease in CSE in the unprepared muscle when the time for action can be anticipated under conditions of low ETU. This relationship further supports the idea that successful selection and execution of actions relies on the activation of the corticospinal representation of the selected action alternative and suppression of the non-selected action, akin to a competitive process through which the appropriate response is ultimately selected (Bestmann et al., 2008; Cisek, 2006, 2007; Cisek & Kalaska, 2010; Julie Duque et al., 2010; Michelet et al., 2010; Reynolds & Ashby, 1999).

This differential activation and suppression of the corticospinal representation of the prepared and unprepared action, respectively, was not influenced by the conditional IS probability (i.e. the hazard rate). This suggests that the differential (de-)activation of action representations reflects event preparation rather than temporal preparation. Importantly, however, event preparation is nevertheless sensitive to the degree of temporal information. Our data show that when participants fail to use the more informative warning cues under conditions of low ETU, then the relative difference in CSE for prepared versus unprepared actions decreases, compared to participants who benefit from low ETU. This suggests that information about time, temporal expectation, or the lack thereof (i.e. temporal uncertainty), interacts with event preparation (see also Chapter 3).

We additionally found that the size of the behavioural benefit under conditions of low ETU is related to the time-course of changes in CSE in the prepared versus unprepared muscle. Here, the relative decrease in CSE in the prepared muscle for early versus late time-points in the preparatory interval was more pronounced in participants with relatively small behavioural effects. In other words, the difference in reaction times for high versus low ETU correlates with the change in CSE over time: a decrease in CSE over time is correlated with reduced benefit of low ETU. This finding speaks against the interpretation that a decrease in CSE reflects an adaptive mechanism that increases the signal-to-noise ratio in the corticospinal representation of the prepared action in anticipation of the voluntary motor command (i.e. *noise reduction*; Hasbroucq et al., 1997; Hasbroucq, Kaneko, et al., 1999; Hasbroucq, Osman, et al., 1999). Contrary to the current data, this account predicts a *decrease* in CSE in the prepared muscle that should relate to an improvement in performance (i.e. larger benefit of low ETU). Instead, the relation that we here observed between the behavioural performance and the neurophysiological correlate supports the idea that inhibitory processes during the FP reflect *impulse control* processes that prevent premature responses (Davranche et al., 2007; Duque & Ivry, 2009; Duque et al., 2010; Sinclair & Hammond, 2008, 2009). If indeed the case, our data suggest that impulse control may come at a prize. We entertain the idea that strong impulse control may cause slower responses to imperative events, an effect that would become evident in cases when advance information about the timing of imperative events (e.g. low ETU) should allow for accurate temporal preparation. A stronger reduction in CSE in the prepared muscle throughout the foreperiod therefore might lead to a smaller difference in reaction times for low versus high ETU.

What neurophysiological mechanisms may account for the changes in CSE that reflect *response competition* and *impulse control*? Facilitatory and inhibitory intra- and inter-cortical circuits shape CSE. Both short (SICI) and long (LICI) intra-cortical inhibition rely on GABA-ergic neurotransmission (Fitzgerald, Maller, Hoy, Farzan, & Daskalakis, 2009), as does the silent period (Davranche et al., 2007). Removal of GABA-ergic inhibition could explain the increase in CSE for selected and prepared actions. Previous work has indeed shown a reduction in SICI and LICI during preparation for action (Sinclair & Hammond, 2008). However, removal of inhibition cannot explain the concomitant suppression in CSE that co-occurs at the same time. Using appropriate paired-pulse TMS techniques that allow for measuring intra- and inter-cortical inhibition and facilitation, future studies may address the neural mechanisms of CSE suppression during action preparation, and how they relate to *impulse control* and *response competition*.

Against our predictions, changes in CSE in Experiment 2 did not reflect the hazard rate. We expected to find a modulation of CSE driven by changes in conditional probability of the IS over time. However, we found no such modulation (for different results, see van Elswijk et al., 2007). Excitatory and inhibitory processes that implement *response competition* and *impulse control* therefore do not appear to be sensitive to changes in IS probability. It is possible, however, that small changes in CSE, driven by changes in IS probability, were masked by processes underlying *response competition* and *impulse control*, in particular as they also influence the time-course of CSE._Future studies may address this issue exploring hazard functions that differ more strongly than in the current experiments, for example, by using uniform versus Gaussian distributions. In this case, the probability density function, cumulative probability, and survival function, which underlie the hazard function, would differ not only in their variability but also in their overall shape. And larger differences may allow finding subtle effects of hazard rate on CSE.

With regard to behavioural data, we also observed a reduction in reaction times on trials when TMS was delivered, as in Experiment 1, which is likely to reflect inter-sensory facilitation (Hashimoto et al., 2004). Importantly, TMS did not modulate the effect of ETU on reaction times. Participants used the same strategy to prepare for imperative events under conditions of ETU irrespective of absence or presence of TMS.

Taken together, selection and preparation of motor actions is supported by a selective increase in CSE in the corticospinal representation of the selected action, and a concomitant decrease for the selected action and non-selected alternative. While the former is not modulated during the preparatory period, CSE suppression increases throughout the foreperiod. Muscle-specific enhancements of CSE are congruent with recent proposals in which actions are selected through a competitive process in which the representation of the most likely action is strengthened (i.e. *response competition*; Bestmann et al., 2008; Cisek, 2007; Cisek & Kalaska, 2005, 2010; Duque et al., 2010; Michelet et al., 2010; Reynolds & Ashby, 1999). Suppression of the non-selected alternative further supports such *response competition* accounts. By contrast, suppression of the selected and prepared action representations is congruent with *impulse inhibition* and *noise reduction* accounts. The contribution of Experiment 2 is to show that information about the timing of impending action interacts with processes underlying *response competition*. When temporal information improves performance, then the relative difference in excitability between prepared and unprepared actions is enhanced throughout the entire preparatory period, predominantly by stronger suppression for the non-selected action._Further, the data suggest that the decrease in CSE throughout the foreperiod may not reflect an adaptive mechanism that increases the signal-to-noise ratio in the motor cortex in preparation for the voluntary motor command (*noise reduction*). More likely, the decrease underlies prevention of premature responses (*impulse control*). A smaller behavioural benefit of advance information about the timing of the imperative event is related to a stronger suppression (i.e. more impulse control). A stronger emphasis on avoiding premature responses may disproportionally affect the condition in which advance information allowed faster responses.

Summary and conclusions

Advance information about impending action improves behavioural performance. In two experiments, we elucidated the electrophysiology of event and temporal preparation for action. Results from Experiment 1 and 2 support the hypothesis that a competitive process supports selection and preparation of the appropriate action alternative (Bestmann et al., 2008; Cisek, 2007; Cisek & Kalaska, 2005, 2010; Julie Duque et al., 2010; Michelet et al., 2010; Reynolds & Ashby, 1999), by selectively increasing CSE for the prepared, and decreasing CSE for the unprepared action representation. The decrease in CSE for the unprepared action occurred either shortly before the IS (Experiment 1), or shortly after the WS when participants experienced ETU (Experiment 2). That is, when participants experience ETU, they initiate inhibitory preparatory processes early on during the FP whereas these processes are delayed until shortly before the IS when its timing is known. While the competitive action selection process is not directly modulated by the probability of occurrence of the imperative event, and how it changes over time (i.e. the hazard function), we show that utilising advance temporal information leads to a stronger suppression for the non-selected action. Information about the timing of forthcoming events thus modulates event preparation.

Second, our findings support the hypothesis that premature responses are prevented by an inhibitory mechanism that selectively suppresses the corticospinal representation of *prepared* actions (Julie Duque & Ivry, 2009; Julie Duque et al., 2010). Such *impulse control* explains the decrease in CSE for the prepared action shortly before the IS when temporal uncertainty was removed (Experiment 1), or shortly after the WS when participants were exposed to temporal uncertainty (Experiment 2).

The correlation between CSE suppression over time with the degree of temporal preparation under conditions of temporal uncertainty (Experiment 2) allows us to distinguish between *impulse control* and *noise reduction*. Only impulse control predicts less suppression for faster responses. This finding further suggests that *impulse control* is influenced by the degree of temporal uncertainty, and that strong impulse control (as reflected in time-dependent decreases in CSE) may even counteract the beneficial effect of reliable temporal information leading to slower responses.

In summary, the present study provides novel insight into the physiological foundations of action preparation. Preparation for action is supported by excitatory and inhibitory processes underlying *response competition* and inhibitory processes underlying *impulse control*. Crucially, we show that information about the *timing* of imperative events interacts with *response competition*. Temporal preparation and event preparation are thus not entirely independent processes.

Chapter 5: The functional contribution of short and long intracortical inhibition to action preparation

Abstract: Preparation for action enables quick responses to imperative events. Inhibitory intracortical circuits in the primary motor cortex (M1) may contribute to action preparation by selectively suppressing the neuronal representation of competing actions (*response competition*), controlling the time of action release by preventing premature responses (*impulse control*), or preventing responses to distracting stimuli (*prevent non-imperative,* cf. *cue activation* Chapter 4). We assessed the functional significance of short (SICI) and long (LICI) intracortical inhibition, as well as their interaction (SICI*LICI), during preparation for action. Transcranial Magnetic Stimulation (TMS) was applied to left M1 during the delay period of an instructed-delay reaction time task 150ms before the imperative stimulus. A warning stimulus instructed preparation for left or right index finger flexion. Motor Evoked Potentials (MEPs) were recorded from the right hand. We found an effector-specific increase in corticospinal excitability (CSE) during preparation for action (i.e. right WS). Further, we found an increase in MEP amplitude for SICI*LICI compared to SICI: LICI inhibits SICI leading to overall disinhibition (net excitation). But neither SICI, LICI, nor the SICI*LICI interaction showed effector-specific modulation during preparation. The increase in CSE during preparation suggests that neural representations of prepared actions are selectively enhanced to ensure quick and efficient execution, consistent with the *response competition*. We speculate that sub-optimal timing of the assessment of intracortical inhibition (i.e. the timing of the TMS) did not allow us to find effector-specific effects for SICI, LICI, and their interaction. We interpret our findings in relation to a neural model of the intracortical circuitry of M1.

Keywords: Transcranial Magnetic Stimulation (TMS), short intracortical inhibition, long intracortical inhibition, action preparation, motor preparation.

Action preparation relies on both excitatory and inhibitory motor circuits (Coxon, Stinear, & Byblow, 2006; Davranche et al., 2007; Duque et al., 2005; Duque & Ivry, 2009; Duque, Lew, Mazzocchio, Olivier, & Ivry, 2010; Floeter & Rothwell, 1999; Hasbroucq, Kaneko, Akamatsu, & Possamaï, 1997, 1999; Reynolds & Ashby, 1999; Sinclair & Hammond, 2008, 2009; van Elswijk, Schot, Stegeman, & Overeem, 2008). Transcranial magnetic stimulation (TMS) allows the non-invasive study of these circuits. Combining two or more TMS pulses in conditioning-test designs allows for probing distinct excitatory and inhibitory circuits (Kujirai et al., 1993; Ziemann et al., 1998). Using this approach, previous work has established the importance of inhibitory circuits in action preparation (Duque et al., 2005; Duque & Ivry, 2009; Duque et al., 2010; Sohn, Wiltz, & Hallett, 2002), though the *specific* functional role of inhibition is still debated. Inhibition may contribute to the selection and preparation of an action by suppressing action alternatives in a competitive selection process (*response competition*; see also Chapter 4; Cisek, 2007; Cisek & Kalaska, 2005; Michelet, Duncan, & Cisek, 2010; van Elswijk, Kleine, Overeem, & Stegeman, 2007). Alternatively, during action preparation, inhibition may prevent the premature release of prepared action (*impulse control*; see also Chapter 4; Floeter & Rothwell, 1999; Hasbroucq et al., 1997, 1999; Reynolds & Ashby, 1999). Finally, inhibition may prevent responses to incidental, non-imperative, and distracting stimuli (*prevent non-imperative*, related to *cue activation* see Chapter 4; Boulinguez, Jaffard, Granjon, & Benraiss, 2008)[2].

At least two different intracortical inhibitory circuits can be assessed with TMS: short (SICI) and long intracortical inhibition (LICI), respectively (Cash, Ziemann, Murray, & Thickbroom, 2010; Kujirai et al., 1993; Sanger, Garg, & Chen, 2001; Ziemann, Rothwell, & Ridding, 1996). Previous work has established that both SICI and LICI are mediated by the inhibitory neurotransmitter γ-aminobutric acid (GABA). The GABA receptor involved in the regulation of neuronal excitability differs for SICI and LICI. SICI is mediated by fast acting $GABA_A$ receptors ($GABA_AR$), whereas LICI predominantly relies on comparatively slow $GABA_B$ receptor mediated neurotransmission ($GABA_BR$; Di Lazzaro et al., 2005, 2007; Di Lazzaro et al., 2006; Florian, Müller-Dahlhaus, Liu, & Ziemann, 2008).

The *functional* significance of SICI and LICI during action selection and preparation remains unclear. The different time courses of $GABA_AR$ and $GABA_BR$ mediated intracortical inhibition (Avoli et al., 1997; Connors et al., 1988; Deisz,

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[2] In Chapter 4, we introduced *cue activation*, a non-motor related explanation of changes in CSE prior to imperative events. According to *cue activation*, CSE increases following the warning cue due to partial, sub-threshold activation of motor pathways elicited by this cue (Boulinguez, Jaffard, Granjon, & Benraiss, 2008). *Prevent non-imperative* is related to *cue activation* but extents to partial activation as a consequence of *any* non-imperative stimulus, not only the warning cue.

1999a, 1999b; McCormick, 1989; McCormick & Williamson, 1989) suggest that LICI and SICI may play different functional roles. SICI could take on a functional role, which requires high temporal precision, such as preventing the premature release of prepared action (*impulse control*; Floeter & Rothwell, 1999; Hasbroucq et al., 1997, 1999; Reynolds & Ashby, 1999) due to the fast response of $GABA_AR$. LICI on the other hand could contribute to the prevention of responses to non-imperative stimuli (*prevent non-imperative*), as this form of inhibition needs to be maintained tonically. And the comparatively slow response of $GABA_BR$ makes LICI a good candidate for functional roles that require tonic suppression. Alternatively, LICI could prevent the execution of non-selected action alternatives by tonically suppressing their neural representations thus contributing to *response competition*.

Recent work has shown that at rest LICI inhibits SICI, possibly pre-synaptically via $GABA_BR$ mediated transmission (Cash et al., 2010; Chu, Gunraj, & Chen, 2008; Florian et al., 2008; Sanger et al., 2001). Thus, when assessing SICI, studying the interaction between LICI and SICI is important, because changes in SICI at rest or during a task can be due to either a genuine change in SICI or changes in LICI, which caused changes in SICI. We therefore assessed the functional role of SICI and LICI as well as their interaction during action preparation. First, we address whether corticospinal excitability (CSE: a measure of the excitability or 'readiness' of M1), SICI, LICI, and their interaction show modulation specific to the effector for which action is prepared. Second, we ask which of the three theories of inhibitory contribution to preparation best explains the observed pattern of modulation, *response competition*, *impulse control*, or *prevent non-imperative* separately for each intracortical inhibitory circuit.

Methods

Subjects

We studied 21 right-handed participants (9 male, mean age 23.4 years, age range 19 – 30 years). All participants were free from known neuropsychological and neuromuscular disorders and had normal or corrected-to-normal vision. Participants gave their written informed consent before participation. The study was approved by a local ethics committee of the UCL Institute of Neurology and in agreement with the declaration of Helsinki.

Electromyographic (EMG) recordings

Surface EMG was recorded from the right first dorsal interosseous (rFDI), stored on a laboratory computer, and subsequently analysed. Additionally, we recorded EMG in the left first dorsal interosseous and the extensor carpi radialis muscle to monitor background EMG activity during the experiment that may contaminate behavioural and physiological data due to differential background muscle activity. EMG was recorded with Ag/AgCl disc electrodes in a tendon-belly montage. EMG was amplified (gain: 1000), band-pass filtered (10Hz – 1 kHz), and digitised (5kHz). During the experiment, EMG was monitored and the experimenter instructed participants to relax when necessary.

Transcranial Magnetic Stimulation

TMS was delivered through a 70mm figure-of-eight coil connected to four monophasic Magstim 200 magnetic stimulators (Magstim, Whitland, Dyfed, UK) via a custom made connector module. This setup allowed us to combine the input of four stimulators and to deliver four pulses at different intensities and / or with different inter-pulse intervals (IPIs) through one stimulator coil. The coil was placed flat on the scalp over the left motor cortex (lM1) with the handle pointing backward and laterally at 45° angle away from the midline. Thus, the current induced in the neural tissue was directed approximately perpendicular to the line of the central sulcus and therefore optimal for activating the corticospinal pathways transsynaptically (Brasil-Neto et al., 1992).

The stimulator coil was moved over the left hemisphere, with fixed slight supra-threshold intensity, to determine the position for eliciting MEPs of optimal amplitude in the rFDI. The optimal position was then marked on the scalp to ensure optimal coil placement throughout the experiment. Subsequently, resting motor threshold (rMT) was determined to the nearest 1% stimulator output. RMT was defined as the lowest intensity required to produce MEPs with an amplitude > 50µV in at least 5 out of 10 consecutive trials (mean = 41.6%, range = 30 – 55%). We similarly determined MT_{1mV} defined as the lowest stimulator output required to produce MEPs of 1mV peak-to-peak amplitude (mean = 44.6%, range = 36 - 62%). Finally, we determined $MT_{1mV/LICI}$ defined as the lowest intensity required to produce MEPs of 1mV peak-to-peak amplitude when preceded by a single TMS conditioning pulse given 100ms earlier at MT_{1mV}, see below (mean = 48.2%, range = 38 - 67%).

Our experimental design included four experimental TMS stimulation conditions: single-pulse TMS (TP_{only}), SICI, LICI, and the combination of SICI and LICI (SICI*LICI; FIG 1). MT_{1mV} intensity was used as the standard test pulse (TP) intensity for SICI (TP_{SICI}), LICI (TP_{LICI}) and for single-pulse TMS (TP_{only}). $MT_{1mV/LICI}$ was used as test pulse intensity in the triple-pulse condition testing SICI*LICI following a protocol used by Sanger and colleagues (Sanger et al., 2001) and Cash et al. (Cash et al., 2010). The underlying rationale of using $MT_{1mV/LICI}$ instead of MT_{1mV} is that the SICI conditioning pulse (CS_2) then acts on the same MEP amplitude in SICI and SICI*LICI – 1mV peak-to-peak. Alternatively, we could have fixed TMS intensity as opposed to MEP amplitude. We decided not to do so, because the LICI conditioning pulse (CS_1) decreases MEP amplitudes (Sinclair & Hammond, 2008). This would have made it difficult to detect a further decrease in MEP amplitude in SICI*LICI during action preparation, a possibility we did not want to exclude beforehand. In any case, intensity adjustments were small (mean % increase = 3.6% stimulator output) and unlikely to be a confound (Garry & Thomson, 2009). For SICI, CS_2 was set at 80 % rMT and the inter-pulse interval (IPI) was set at 2ms (Chu et al., 2008; Kujirai et al., 1993). For LICI and SICI*LICI, CS_1 was set at $MT_{1mV,}$ using an IPI of 100ms. This protocol is known to yield strong inhibition when applied on its own, and to cause disinhibition when the test pulse is preceded by CS_1 and CS_2 during rest (Sanger et al., 2001).

Additionally, we included two TMS control conditions (Figure 5.1). First, $LICI_{control}$ to assess whether our efforts to match MEP amplitudes in SICI and SICI*LICI were successful throughout the experiment. In $LICI_{control}$, we used $MT_{1mV/LICI}$ as a test pulse, and MT_{1mV} as CP_1 with an IPI of 100ms. Second, we included a stimulation condition in which CP_1 was applied without subsequent test pulse (i.e. 250ms before IS: $CS_{1\ only}$). We included this condition, because otherwise CP_1 could have been informative about the timing of the IS and thus have biased participants' preparation for future action. Essentially, we wanted to prevent participants from waiting with their action preparation until after TMS was delivered. For the same reason, we also included trials without TMS stimulation.

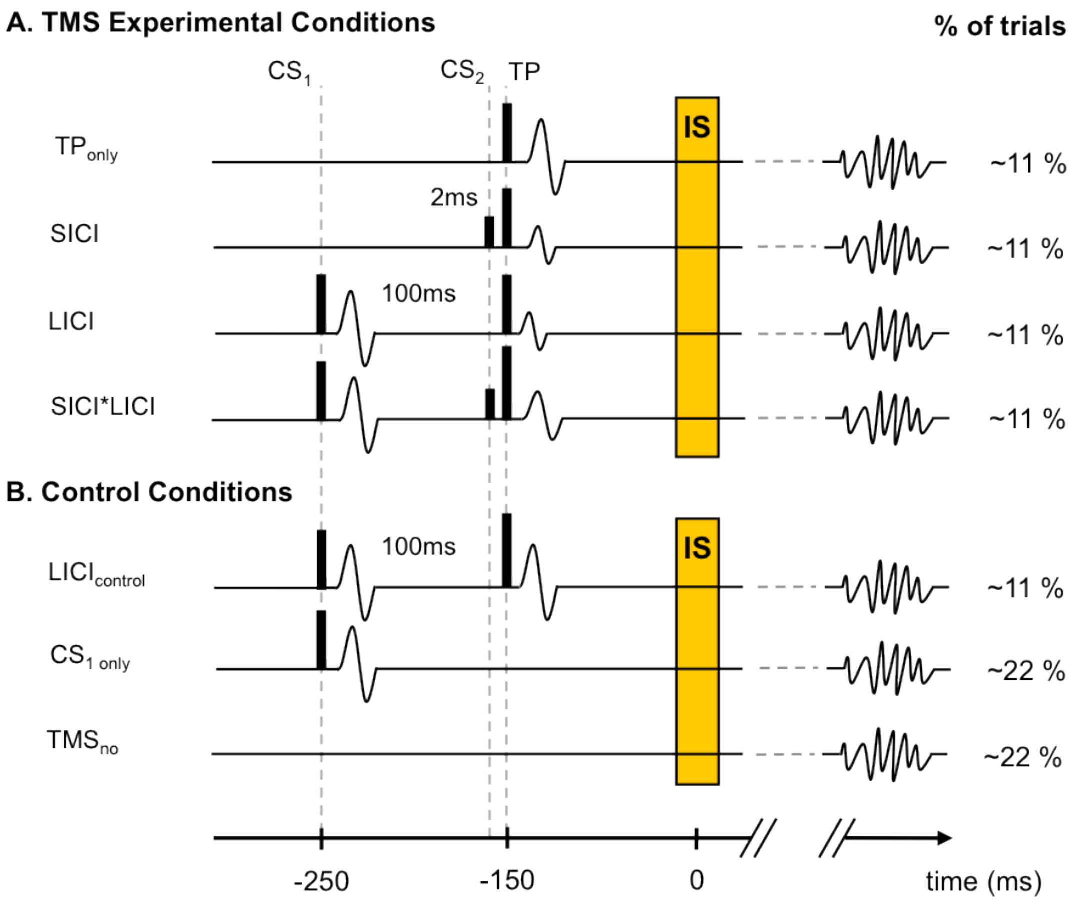


Figure 5.1: Schematic illustration of the Transcranial Magnetic Stimulation (TMS) conditions. (A) For the TP_{only} condition, a single supra-threshold TMS pulse (TP) was given 150ms before the imperative stimulus (IS) at the TMS intensity required to elicit Motor Evoked Potentials (MEP) of 1mV peak-to-peak amplitude (MT_{1mV}). To assess $GABA_AR$ mediated short intracortical inhibition (SICI), a TP at MT_{1mV} was preceded by a single sub-threshold TMS conditioning pulse (CS_2) at 80% MT_{1mV} by 2ms. To assess $GABA_BR$ mediated long intracortical inhibition (LICI), a TP at MT_{1mV} was preceded by a single supra-threshold TMS conditioning pulse (CS_1) at MT_{1mV} by 100ms. A combination of the SICI and LICI protocol was employed to assess the interaction between SICI and LICI (SICI*LICI). A single sub-threshold TMS conditioning pulse (CS_2) at 80% MT_{1mV} was inserted 2ms before TP into the LICI protocol. For SICI*LICI, TP was given at $MT_{1mV/LICI}$ which was set to evoke 1mV peak-to-peak MEP amplitudes if preceded by CS_1.This ensured that CS_2 acted on the same peak-to-peak MEP amplitudes in SICI and SICI*LICI. **(B)** Control conditions: $LICI_{control}$ was a modification of the LICI protocol. CS_1 preceded TP by 100ms, as in the LICI protocol, but TP was given at $MT_{1mV/LICI}$. This condition was included to assess whether MEP amplitudes in SICI and SICI*LICI were sufficiently matched throughout the experiment. Additionally, we included trials with CS1 only ($CS_{1\ only}$) and trials without TMS stimulation (TMS_{no}) to reduce the predictability of the IS based on the delivery of TMS.

Experimental design

Participants sat comfortably in front of a computer screen at approximately 70 cm viewing distance. Participant's left and right index fingers were resting on the left and right buttons of a custom-made button box. Their hands were placed so that they could comfortably press the buttons without pre-contraction of the target muscle. A comfortable chair as well as arm support furthermore ensured that participants could relax throughout the experiment. Stimuli were presented using Matlab and the Cogent2000 toolbox (University College London, http://www.vislab.ucl.ac.uk/Cogent2000/index.html).

We used a basic instructed-delay reaction time task (see Figure 5.2). After a brief presentation of a fixation cross (200ms) to indicate the start of a trial, participants received the warning stimulus (WS), an arrow pointing either to the left (42% of all trials) or to the right (42% of all trials). The WS informed participants about future action and was included to prompt preparation for action. The WS was presented for 500ms and then replaced by the fixation cross. After a fixed delay of 1500ms the imperative stimulus (IS) appeared. The IS was a circle either to the left or to the right of the fixation cross, instructing a left-hand or right-hand button press, respectively. Participants were instructed to respond as fast as possible, but not at the expense of accuracy. The WS was always valid, thereby reliably indicating future action and thus allowing preparation for action.

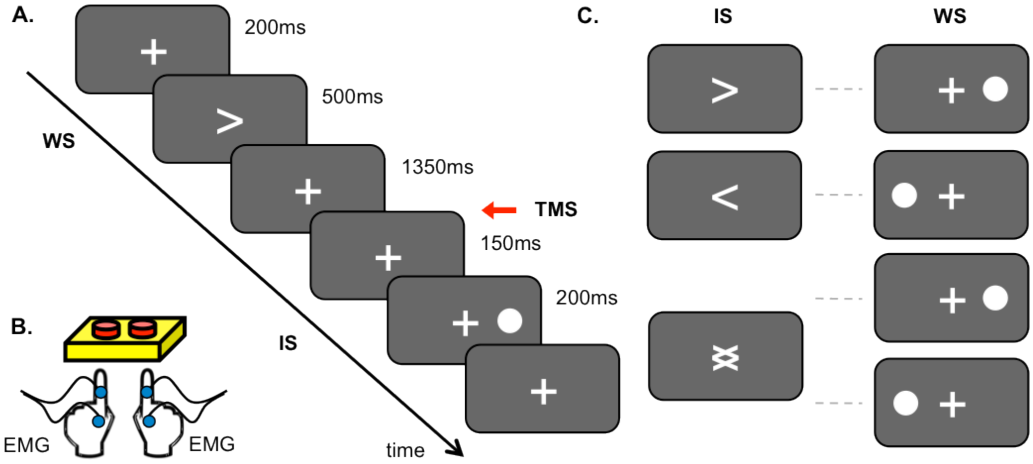


Figure 5.2: Experimental design and setup. (A) Timeline. Participants were instructed to prepare either left or right index finger flexion based on the warning stimulus (WS) and to respond as quickly as possible to a subsequent imperative stimulus (IS). Feedback about average mean reaction times (RT) was given every 25 trials during the inter-trial interval (ITI). The test pulse (TP) was always applied 150ms before IS. **(B)** Motor-evoked potentials were recorded from the right first dorsal interosseous (rFDI) muscle. Additionally, EMG was recorded from the left FDI and right extensor carpi radialis to monitor background EMG activity in both hands. **(C)** The different combinations of WS and IS included informative and non-informative trials. WS, if informative, was always reliable. The non-informative WS was included to test for an increase in RT compared to informative WS to infer action

Additionally, we included two types of control trials. First, on 16 % of all trials, the WS consisted of an arrow pointing both to the left and to the right and was thus non-informative about the future action. Nevertheless, participants had to respond as quickly as possible to the IS. Comparing reaction times between informative and uninformative cues allowed us to confirm whether participants used informative cues to prepare the appropriate action in advance. Second, to prevent premature responses, we included 16% of catch-trials in which participants received either an informative (80%) or a non-informative (20%) WS, but no IS. Participants were instructed to withhold a response if no IS was presented. On all trials, except catch trials, participants were encouraged to respond as quickly and as accurately as possible. Every 15 trials, they received feedback about their average reaction time over the last 15 trials to motivate quick and consistent responses throughout the experiment.

The specific stimulation condition for catch and non-informative control trials was randomly sampled from all available stimulation conditions, including non-TMS trials. The proportion of TMS trials thus varied slightly across blocks and participants. On 22% of trials, participants did not receive TMS, and on a further 22% of trials participants received CS_1 only ($CS_{1\ only}$). On the remaining trials, participants received either TP_{only}, SICI, LICI, SICI*LICI, or $LICI_{control}$, respectively (see Figure 5.1). Thus, participants received CS_1 (250ms before IS: $CS_{1\ only}$, LICI, LICI*SICI, $LICI_{control}$) on 56%, and no CS_1 on 44% of trials (TP_{only}, SICI, TMS_{no}). If participants did not receive CS_1 (TP_{only}, SICI, TMS_{no}), then there was a 50% chance to receive late TMS stimulation (CS_1 and / or TP 152/50ms before IS: SICI, TP_{only}). If participants had received CS_1 (LICI, SICI*LICI, $CS_{1\ only}$) then there was a 40% chance of receiving no further TMS ($CS_{1\ only}$). The inclusion of these trials at the given percentages avoided predictability of the IS based on TMS delivery. When delivered, the TMS test pulse occurred at 150ms and CS_1 occurred 250ms prior to the imperative stimulus.

The experiment consisted of 6 blocks of 74 trials each. Each experimental block was preceded by verification of correct coil placement, the correct intensity of $MT_{1mV/LICI}$ and, if necessary, TMS intensity adjustment (for $MT_{1mV/LICI}$ only) to guarantee matched amplitudes throughout the experiment. Before and after each experimental block, we recorded two MEP traces for each TMS stimulation condition (= 10 trials) to confirm accurate coil placement and that CS1 and CS2 (SICI, LICI) intensities remained appropriate. Participants were given a short training session of 20 trials before the experiment to familiarise themselves with the task, including the measurements before and after each experimental block, and to get used to the TMS stimulation.

Data processing and statistical analysis

We excluded all trials with premature responses (reaction times < 100ms). Additionally, we excluded trials with incorrect behavioural responses (e.g. a left hand response for a right hand IS), and response omissions. Subsequently, Grubb's test

($\alpha = 0.05$) was used on remaining trials to determine and exclude outliers in reaction times. If after exclusion overall error exceeded 20% of all trials, we excluded the full dataset of the participant from further analysis. To test whether participants prepared following informative WSs we ran a 3 x 1 within subject repeated measures ANOVA on mean reaction times with the factor cue (informative right, informative left, non-informative). Paired two-tailed t-tests were used to further explore effects.

For trials with TMS stimulation, we extracted MEP peak-to-peak amplitudes as well as pre-TMS EMG activity from the EMG traces recorded in rFDI. We excluded all trials with a MEP amplitude below 0.1mV (Mars et al., 2007). As pre-TMS EMG activity is known to affect MEPs (Duque et al., 2005; Duque et al., 2010), we excluded all trials with a root mean square of pre-TMS EMG activity exceeding 0.05mV measured over a time window 100ms prior to the first TMS pulse. Subsequently, to ensure that pre-TMS EMG activity was similar across all conditions, we ran Grubb's test ($\alpha = 0.05$) on the root mean square of pre-TMS EMG on all trials for each subject separately to determine and exclude any outliers in pre-TMS EMG activity. The limited number of trials in each experimental condition did not allow us to exclude outliers in peak-to-peak MEP amplitudes in each condition separately. Excluding outliers across conditions may have biased results. Hence, all further analyses were run on median MEP amplitudes in order to reduce the effect of possible outliers in the data (Livingston & Ingersoll, 2008).

Since we stimulated the left hemisphere, trials where a right cue was presented as the WS should reveal neural effects of action preparation, relative to trials where a left cue was presented as the WS. This approach controls for possible non-specific effects of action preparation, such as arousal and attention.

First, we assessed whether action preparation modulates CSE and whether MEP amplitude evoked in TP_{only} and $LICI_{control}$ were matched. We computed 2 x 2 within subject repeated measures ANOVA on median MEP amplitude evoked in

TP_{only} and $LICI_{control}$ with WS (left, right) and TMS (TP_{only}, $LICI_{control}$) as factors (for illustrative single trial MEP traces, see Figure 5.3).

Second, we explored whether action preparation modulates SICI, LICI, or the interaction between SICI and LICI. We divided MEP amplitude evoked in SICI, LICI, or SICI*LICI by the median MEP amplitude in TP_{only} for each WS (left, right) and participant separately, because the strength of SICI, LICI, or SICI*LICI, is expressed as the percentage reduction in median MEP amplitude compared to $TP_{only:}$ Then, to explore the modulation of SICI, LICI, and SICI*LICI by preparation for action, we computed a 2 x 3 within subject repeated measures ANOVA on normalised MEP amplitudes with the factors WS (left, right), and TMS (SICI, LICI, SICI*LICI).

Finally, we verified that MEP amplitude was indeed reduced in SICI, LICI, and SICI*LICI. Normalised MEP amplitude was tested against one using 6 one-sample t-tests. Statistical threshold was set at 0.05 and corrected for multiple comparisons, whenever appropriate, using Bonferroni-correction. If a significant Mauchly's tests revealed a violation of the sphericity assumption, then degrees of freedom were adjusted using Greenhouse-Geisser.

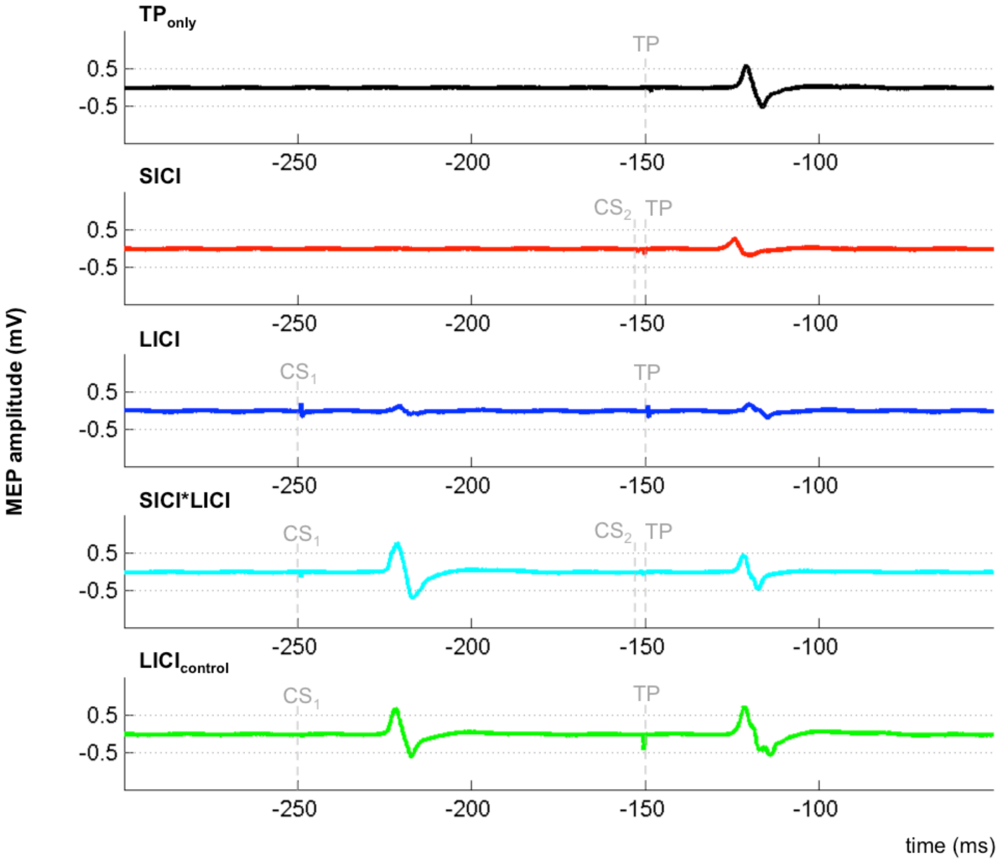


Figure 5.3: Single EMG traces for each TMS condition for warning stimuli (WS) indicating right index finger flexion. Single EMG traces illustrate single trial peak-to-peak MEP amplitudes evoked in TP$_{only}$, SICI, LICI, SICI*LICI, and LICI$_{control}$. In SICI and LICI, peak-to-peak MEP amplitudes were reduced compared to TP$_{only}$. In TP$_{only}$ and LICI$_{control}$, the peak-to-peak MEP amplitudes evoked by the TP were approximately equal.

Results

Exclusion of trials or datasets

Based on behavioural performance, we excluded one participant with an error rate exceeding 20% of trials. Additionally, we excluded one further participant because after exclusion of MEP traces following the criteria given above no trials were left in one of our experimental conditions. Overall, we excluded 13.0 % of all trials due to either behavioural error (omissions: 1.3 %, incorrect key presses: 0.5 %, RT < 100ms: 4.1 %), small MEP amplitude (4.8 %), or pre-TMS EMG activity (2.4 %).

Reaction time task

The 3 x 1 repeated measures ANOVA on mean reaction times was significant ($F_{(1.15,20.77)} = 43.68$, $p < 0.001$, $\eta_p^2 = 0.708$). If the WS was non-informative, participants responded slower to imperative events (*mean = 271.4ms, SE = 9.3)* compared to informative WSs indicating either left *(mean = 238.1ms, SE = 6.3;* $t_{(18)} = -7.34$, $p < 0.001$) or right *(mean = 239.0ms, SE = 6.1;* $t_{(18)} = -6.34$, $p < 0.001$) index finger flexion. Reaction times between left and right index finger responses did not differ ($t_{(18)} = -0.56$, $p = 0.585$; see Figure 5.3).

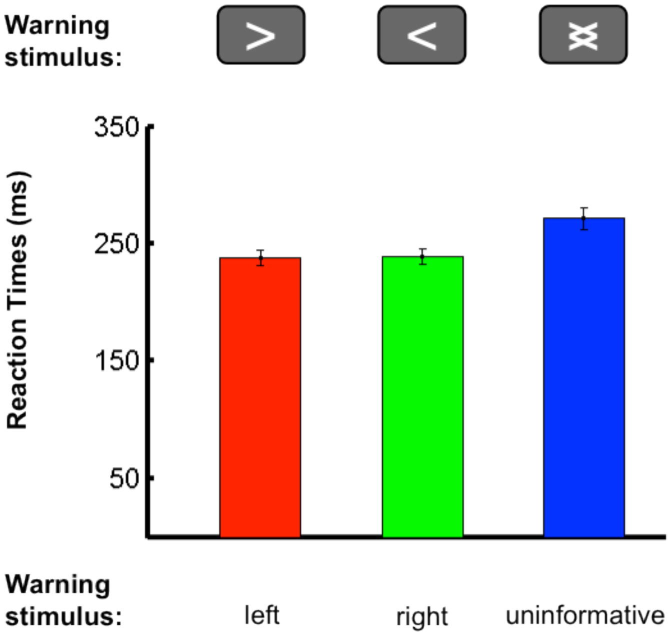


Figure 5.4: Reaction times. Responses to imperative events were faster if events were preceded by informative versus uninformative warning stimuli (WS). There was no difference between responses with the left or right index finger if preceded by informative WS.

CSE and manipulation check: TP_{only} & $LICI_{control}$

If the WS indicated a right compared to a left hand response, then the median MEP amplitude increased ($F_{(1,19)}$ = 12.70, p = 0.002, η_p^2 = 0.401). There was no difference between TP_{only} and $LICI_{control}$ ($F_{(1,19)}$ = 0.49, p = 0.491, η_p^2 = 0.025) and no interaction between the type of TMS (TP_{only} / $LICI_{control}$) and the WS ($F_{(1,19)}$ = 0.04, p = 0.849, η_p^2 = 0.002; see Figure 5.4).

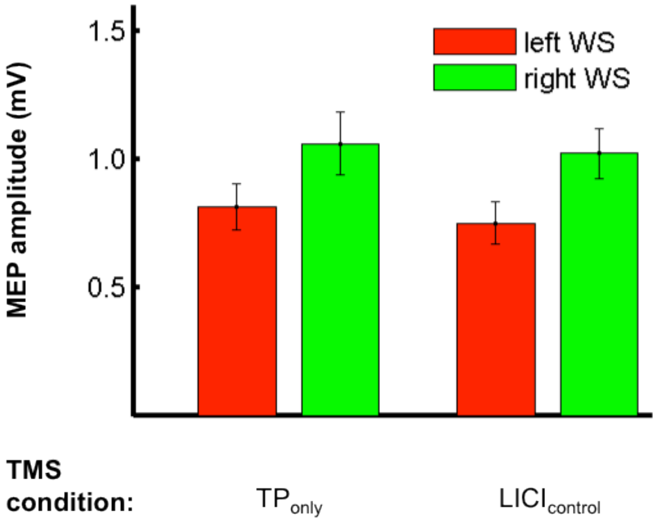


Figure 5.5: Results for TP_{only} and $LICI_{control}$. The graph shows the median amplitude of Motor Evoked Potentials (MEPs) averaged across participants for TP_{only} (left) and $LICI_{control}$ (right) for warning stimuli (WS) indicating left (red) or right (green) index finger flexion. Corticospinal excitability (CSE), reflected by MEP amplitude, increased in the corticospinal representation of the right first dorsal interosseous (rFDI) following right versus left WS. There was no difference between TP_{only} and $LICI_{control}$.

*SICI, LICI, and their interaction (SICI*LICI)*

The type of stimulation, SICI, LICI, or SICI*LICI, had a significant effect on normalised median MEP amplitude ($F_{(2,38)}$ = 6.66, p = 0.003, η_p^2 = 0.259). Normalised median MEP amplitude was increased for SICI*LICI (*mean = 0.81mV, SE = 0.09*) compared to SICI (*mean = 0.57mV, SE = 0.07;* $t_{(18)}$ = 0.238, p = 0.006) or LICI (*mean = 0.53mV, SE = 0.06;* $t_{(18)}$ = 0.281, p = 0.010). But the WS had no effect on normalised median MEP amplitude ($F_{(1,19)}$ = 0.17, p = 0.683, η_p^2 = 0.009). Also, the interaction between WS and TMS was not significant $(F_{(2,38)} = 0.45, p = 0.641, \eta_p^2 = 0.023$; see Figure 5.5).

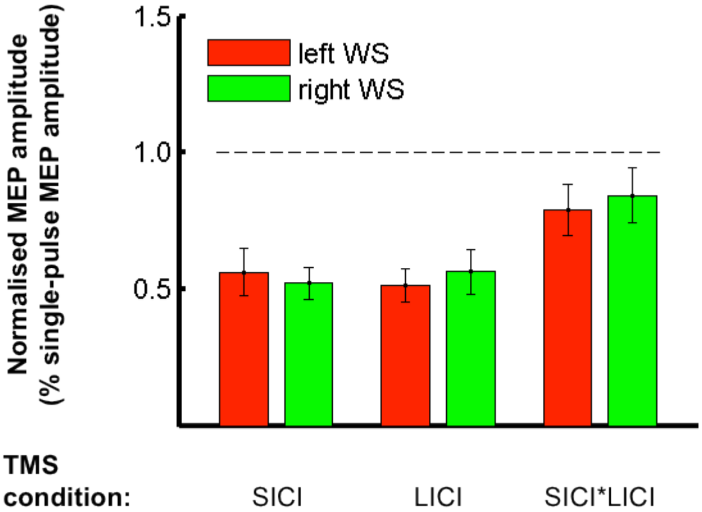


Figure 5.6: Modulation of SICI, LICI, and their interaction (SICI*LICI) during action preparation. The graph shows the median amplitude of Motor Evoked Potentials (MEPs) evoked in SICI, LICI, or SICI*LICI as a percentage of the median MEP amplitude evoked in TP_{only}. CS_2 for SICI, CS_1 for LICI, and CS_1 and CS_2 combined for SICI*LICI reduced MEP amplitude. For SICI*LICI versus SICI or LICI this reduction was for smaller suggesting disinhibition. There was no effector-specific modulation of SICI, LICI, or SICI*LICI by left (red) or right (green) warning stimuli.

The CS_1 (LICI), CS_2 (SICI), and the combined CS_1 and CS_2 (SICI*LICI) lead to a significant reduction in MEP amplitude for both left and right WS $(SICI*WS_{left}: t_{(18)} = 6.33, p < 0.0001; SICI*WS_{right}: t_{(18)} = 8.69, p < 0.0001; LICI*WS_{left}: t_{(18)} = 8.18, p < 0.0001; LICI*WS_{right}: t_{(18)} = 6.81, p < 0.0001; SICI*LICI*WS_{left}: t_{(18)} = 8.26, p < 0.0001; SICI*LICI*WS_{right}: t_{(18)} = 8.40, p < 0.0001$; see Figure 5.5 and 5.6).

Discussion

The present study assessed SICI, LICI as well as their interaction (SICI*LICI) during preparation for action with the overall aim to elucidate the functional contribution of $GABA_AR$ (SICI) and $GABA_BR$ (LICI) mediated intracortical inhibition to preparation for action. Intracortical inhibition may contribute to action preparation by selectively suppressing the neuronal representation of competing actions (*response* *competition*), controlling the time of action release (*impulse control*), or preventing responses to distracting, non-imperative stimuli (*prevent non-imperative,* cf. *cue activation* in Chapter 4).

We found an effector-specific increase in corticospinal excitability (CSE) in the corticospinal representation of rFDI when a preceding WS indicated right compared to left index finger flexion. In addition, we found disinhibition of SICI by LICI reflected by an increase in MEP amplitude when LICI conditioning pulse preceded SICI (CS_1: SICI*LICI). However, there was no evidence for an effector-specific modulation of SICI, LICI, or their interaction by a preceding left or right WS.

The effector-specific increase in CSE during action preparation supports the hypothesis that during preparation the excitability of action representations required for the selected and prepared action alternative increases selectively (*response competition*; Cisek, 2007; Cisek & Kalaska, 2005; Michelet et al., 2010; van Elswijk et al., 2008). The data suggest that this increase in CSE is not due to an effector-specific removal of inhibition. In the current sample, LICI decreased only slightly during preparation for action in the prepared effector. Such a slight reduction in inhibition, which in this dataset was not statistically significant, cannot convincingly explain the clear and significant modulation of CSE duration action preparation. Similarly, the lack of an effector-specific effect for SICI cannot explain the modulation of CSE during action preparation. On the contrary, in the current sample, SICI was slightly elevated during preparation for action (albeit not significantly). Increased SICI could only explain a *decrease* in CSE during preparation for action. Instead of inhibitory circuits, facilitatory circuits may be responsible for increasing the neuronal excitability during preparation for action, for example, intracortical facilitation (ICF) or short intracortical facilitation (SICF). Future research may address the potential functional significance of intracortical facilitation during preparation for action. Importantly, facilitatory circuits, as assessed with TMS, interact with both facilitatory and inhibitory circuits. For example, SICI is known to facilitate SICF while ICF inhibits SICF (Wagle-Shukla, Ni, Gunraj, Bahl, & Chen, 2009).

Our data show that SICI is inhibited by LICI. This constitutes a *removal* of net inhibition (i.e. disinhibition) in SICI*LICI reflected by an overall increase in CSE. This increase in CSE cannot be attributed to higher MEP amplitude in SICI*LICI compared to SICI as we ensured that CS_2 acted on comparable MEP amplitude in SICI and SICI*LICI. Therefore, this finding reveals, for the first time, that SICI and LICI interact when participants are engaged in a cognitive task. Previous studies have found such interaction at rest only (Cash et al., 2010; Sanger et al., 2001). However, there was no effector-specific modulation of this disinhibition: the strength of disinhibition in the corticospinal representation of rFDI did not differ during preparation for left versus right index finger flexion. Similarly, we found no evidence for an effector-specific modulation of SICI and LICI during preparation for action. As expected, we did find a substantial reduction in MEP amplitude by the CS_2 for SICI and the CS_1 for LICI. There was SICI and LICI while participants were performing the task. However, differences in SICI and LICI during preparation for right versus left index finger flexion were too small to reach significance.

However, the numerical pattern of our data does match the initial hypotheses, despite not reaching statistical significance. Based on the time course of $GABA_AR$ and $GABA_BR$ mediated intracortical inhibition, we speculated that SICI controls the well-timed release of prepared actions by preventing premature responses (*impulse control*). Consequently, we expected an increase in SICI, expressed by a stronger reduction in MEP amplitude, during preparation for action close to the imperative event. Albeit not significant, in the current sample, SICI increased during preparation for action. Previous studies have reported effector-specific removal of SICI during the RT period *after* presentation of the IS, shortly before action execution (Floeter & Rothwell, 1999; Reynolds & Ashby, 1999; Y. H. Sohn et al., 2002). In addition, studies using stop-signal tasks have demonstrated the importance of SICI in volitional inhibition of a prepared response (Y. H. Sohn et al., 2002) when the release of the prepared action has to be prevented after the imperative stimulus has been shown. Our data show that SICI may have functional relevance during preparation for action, too, in particular preventing the premature release of prepared actions. The fast response of $GABA_AR$ mediated intracortical inhibition makes it a good candidate indeed for controlling the release and timing parameters of actions (Avoli et al., 1997; Connors et al., 1988; Deisz, 1999a, 1999b; McCormick, 1989; McCormick & Williamson, 1989).

Based on the comparatively slow response of $GABA_BR$, we speculated that LICI might prevent responses to non-imperative signals (such as the WS: *prevent non-imperative*), or alternatively, suppresses representations of unselected action alternatives (*response competition*) because both alternatives require *tonic* inhibition. *Prevent non-imperative* predicts a gradual removal of LICI, expressed by a smaller reduction in MEP amplitudes, during preparation for action as the probability of the imperative event increases, in particular for the prepared response. Similarly, for the prepared response, *response competition* predicts a gradual removal of LICI and for the unprepared response a gradual increase in LICI as the probability of the imperative event increases. Indeed, though not significant, LICI was reduced during preparation for action (for similar results, see Sinclair & Hammond, 2008). This finding is compatible with both *prevent non-imperative* and *response competition*. LICI may either prevent responses to non-imperative stimuli or contribute to action selection by suppression cortical representations of non-selected action alternatives. However, the clear effector-specific modulation of CSE during action preparation suggests that another mechanism, perhaps in addition to LICI (e.g. ICF), also contributes to *response competition*.

Studies on SICI, LICI, and their interaction during rest have inspired models of intracortical connectivity in M1 (Sanger et al., 2001). Our data support these models: SICI and LICI decrease the output of I-wave generating neurons thereby reducing CSE. LICI interacts with SICI by decreasing the effect of SICI on CSE (Figure 5.7).

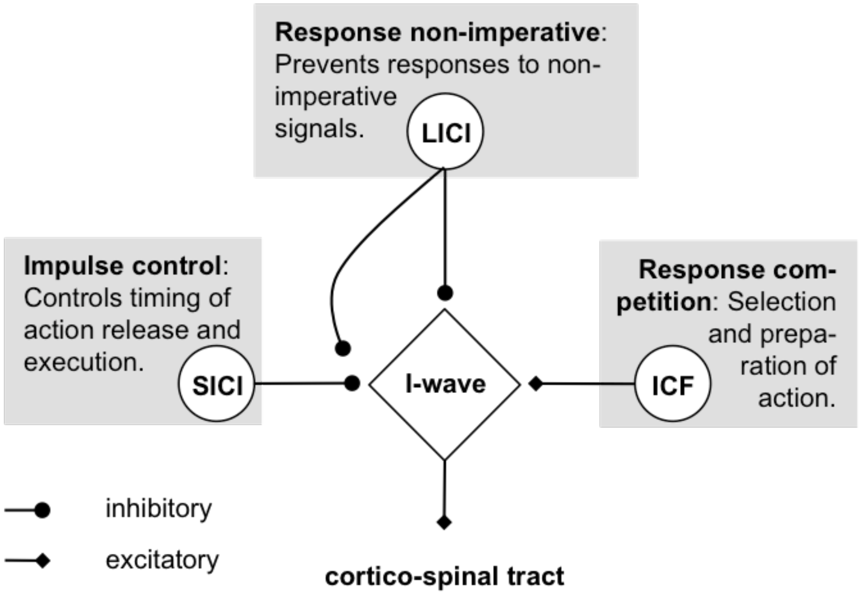


Figure 5.7: Schematic model of the intracortical circuitry of the primary motor cortex (M1) and their functional contribution to action preparation. The initial model of the intracortical circuitry in M1 was developed based on data acquired at rest (see Sanger et al., 2001). Our data support this model: SICI and LICI decrease the output of I-wave generating neurons reducing corticospinal excitability (CSE). LICI interacts with SICI, possibly via pre-synaptic GABA$_B$R mediated neuronal transmission. LICI decreases SICI and thus leads to an increase in CSE by removal of SICI (i.e. disinhibition). During action preparation, an effector-specific increase in CSE suggests that the neural representation of the prepared action is selectively activated (*response competition*). We speculate that intracortical facilitation (ICF) may support effector-specific increases in CSE. We found no effector-specific modulation of SICI or LICI. We speculate that SICI controls the release of action initiation and execution to ensure the correct timing of actions (*impulse control*). We speculate that LICI prevents responses to non-imperative events. Future experiments will have to confirm these hypotheses. If SICI controls the timing of the release and execution of actions, then SICI should increase during action preparation in an effector-specific way (*impulse control*). If LICI prevents actions either when an action needs to be withheld or to the occurrence of non-imperative but distracting stimuli (*prevent non-imperative*), then LICI should increase when the IS is not likely to occur, i.e. early during the delay, and decrease as the likelihood of occurrence of IS increases.

Models of intracortical connectivity in M1 offer a useful framework for interpreting our results. ICF may be involved in selectively enhancing, or suppressing, the neural representations of selected or unselected action alternatives underlying the reported modulation in CSE. SICI may underlie the controlled and well-timed release of prepared actions (*impulse control*). LICI may prevent responses to distracting, non-imperative events (*prevent non-imperative*). However, in the current study, the effector-specific modulations of SICI, LICI, and their interaction were small and failed to reach statistical significance. We probed CSE, SICI, LICI, and their interaction shortly before the arrival of the IS. Ideally, one would study the development of CSE and intracortical inhibition during the entire preparatory period and not only at one isolated time-point. In the current study, the particular moment in time when CSE and intracortical inhibition were probed may have been sub-optimal. Possibly, at other time-points, one could have found clear effector-specific modulations of SICI, LICI, and their interaction. In particular, if LICI was involved in preventing responses to distracting events, it should show strongest effector-specific modulation early on during the preparatory period. SICI should be strongest just before the IS, if preventing the premature release of prepared actions (*impulse control*). The time when we probed intracortical inhibition in the current study may have been too late for LICI and too early for SICI to find effector-specific modulation. Future studies that probe CSE and intracortical inhibition at several time-points during the preparatory period will have to explore this possibility. Such studies are relevant for our understanding of the functional significance of inhibitory and excitatory circuitry in M1. They allow the integration of models of the intracortical circuitry in M1 with classic behavioural paradigms used for studying manual actions, which may allow establishing the relation between abnormalities in intracortical circuitry and behavioural symptoms in disease in the future.

Chapter 6: Distortion of *external* but not *internal* temporal uncertainty in reward-based decision making

Abstract: Part of the uncertainty surrounding the outcome of an action is *external*, due to stochastic variability in the environment, and part is *internal*, due to sensorimotor "noise". In this study, we asked whether observers could select actions that correctly compensate for combinations of external (ETU) and internal timing uncertainty (ITU) to maximise expected reward. We first trained participants on a time interval estimation task. They received reward when their estimate fell inside a brief reward-window. ETU was manipulated by stochastically varying the timing of the reward-window around the target interval (TI). ITU was manipulated by increasing the duration of the TI. Following this training, participants chose between pairs of stimuli varying in ITU and ETU including novel combinations not encountered during training. We compared human performance to that of an ideal observer who selects ITU / ETU combinations with lower temporal uncertainty and consequently, a higher probability of reward. Observed behaviour differed from optimal performance due to biased estimates of ETU while estimates of ITU were highly accurate.

Keywords: Statistical decision theory, Bayesian decision theory, timing, temporal uncertainty, optimal statistical models, interval reproduction

Combining uncertainty from external and internal sources to estimate the expected costs and benefits is a key challenge in deciding between alternative actions. In this chapter, we examine the ability to estimate and combine internal and external *temporal* uncertainty in a reward-based decision making task that puts a premium on the accurate timing of motor actions. Under conditions of external risk and uncertainty (Allais, 1953; Friedman & Savage, 1948; Kahneman & Tversky, 1979; Kahneman & Tversky, 2000; Lichtenstein, Slovic, Fischhoff, Layman, & Combs, 1978; Tversky & Kahneman, 1992), participants typically exhibit patterned deviations from optimal performance. In particular, participants overestimate the probability of infrequent events and display risk aversion (Tversky & Kahneman, 1992). By contrast, under conditions of internal uncertainty (Trommershäuser et al., 2003, 2008) participants typically, but not always (Trommershäuser, 2009), select actions that take into account their own visual and motor uncertainties and come close to maximizing expected reward (Gepshtein et al., 2007; Seydell et al., 2008; Trommershäuser et al., 2005, 2006).

Crucially, learning about one's own internal uncertainty differs from learning about environmentally induced external uncertainty. Participants know about their own internal uncertainty from experience. By contrast, in typical economic choice tasks, all possible outcomes and their respective probabilities are explicitly communicated to the decision-maker: participants might be offered a choice between 10% chance of winning $5000 (90% winning nothing) and a 95% change of winning $300 (5% change winning nothing; Trommershäuser et al., 2008).

When participants make decisions under conditions of external uncertainty based on *experience* (i.e. repeated sampling of the available options), they typically *under*estimate the probability of rare events (Hau, Pleskac, Kiefer, & Hertwig, 2008; Hertwig & Erev, 2009). Increasing the sample size reduces this discrepancy between decisions based on experience versus decisions based on explicit descriptions (Rakow, Demes, & Newell, 2008). A recent study has found that, when given the opportunity to draw large representative samples in little time, participants neither over- nor underweight small probabilities (Hilbig & Glöckner, 2011).

Can we thus explain optimal performance on motor-lotteries and sub-optimal performance on economic decision tasks by this difference in how we learn the level of internal or external uncertainty that we are exposed to? The answer is: probably not! While participants require extensive training to achieve optimal performance on economic decision tasks based on experience (Hilbig & Glöckner, 2011), participants perform close to optimal right from the start on unfamiliar and highly artificial visuo-motor decision tasks (Trommershäuser et al., 2006). However, to directly compare choice under external and internal uncertainty, one has to match the learning process for external and internal uncertainty and then compare their effects on behaviour in a single experiment.

We developed a novel paradigm to explore choice under conditions of *both* internal (ITU) and external (ETU) temporal uncertainty. Participants learned about both ETU and ITU by repeated sampling during training with feedback. Following training, they repeatedly chose between two options that differed in ETU, ITU, or both, now without feedback. We asked, first whether participants could combine estimates of ETU and ITU for choice, and second, whether participants' estimates of ETU and ITU were biased.

We compared observed versus predicted optimal performance to address the latter question. Formally, ITU is a Gaussian random variable whose standard deviation grows linearly with time interval duration. It depends entirely on participants' accuracy in time interval estimation. By contrast, ETU is under experimental control. In the present study, ETU was manipulated to also resemble a Gaussian random variable. Participants had to choose between executing of one out of two possible actions. Each action was the reproduction of a target interval (TI) of a particular duration and could potentially lead to a reward. Two factors affected the probability of reward. The first was the duration of the TI: as ITU increases with increasing time interval duration, participants were less likely to accurately reproduce longer TIs. Second, the appropriate time for action was varied unpredictably from one trial to the next. While participants were instructed to reproduce the TI, the appropriate time to respond to receive reward was sometimes earlier and sometimes later than the indicated TI, which constituted our manipulation of ETU. Evidently, participants were more likely to be rewarded for short TIs, due to greater precision in time estimation, and under conditions of low levels of ETU, due to less variability in the external world.

In choice, we asked participants to consider two hypothetical time interval reproduction trials, which varied in ETU, ITU, or both. Participants did not attempt to execute either trial; they simply chose which of the two they would prefer to execute. They were told that they would be allowed to execute the chosen configuration on a small number of randomly chosen trials and receive monetary rewards if they responded at the right time ($0.25). The probability of reward was determined by the sum of ITU and ETU, the total timing uncertainty, $\sigma_{TU} = \sqrt{\sigma_{ITU}^2 + \sigma_{ETU}^2}$. It was to the participant’s advantage on each trial to select the configuration (combination of ITU and ETU) that was lower in overall temporal uncertainty. Figure 6.1 shows indifference contours and optimal choice for a variety of different decision scenarios.

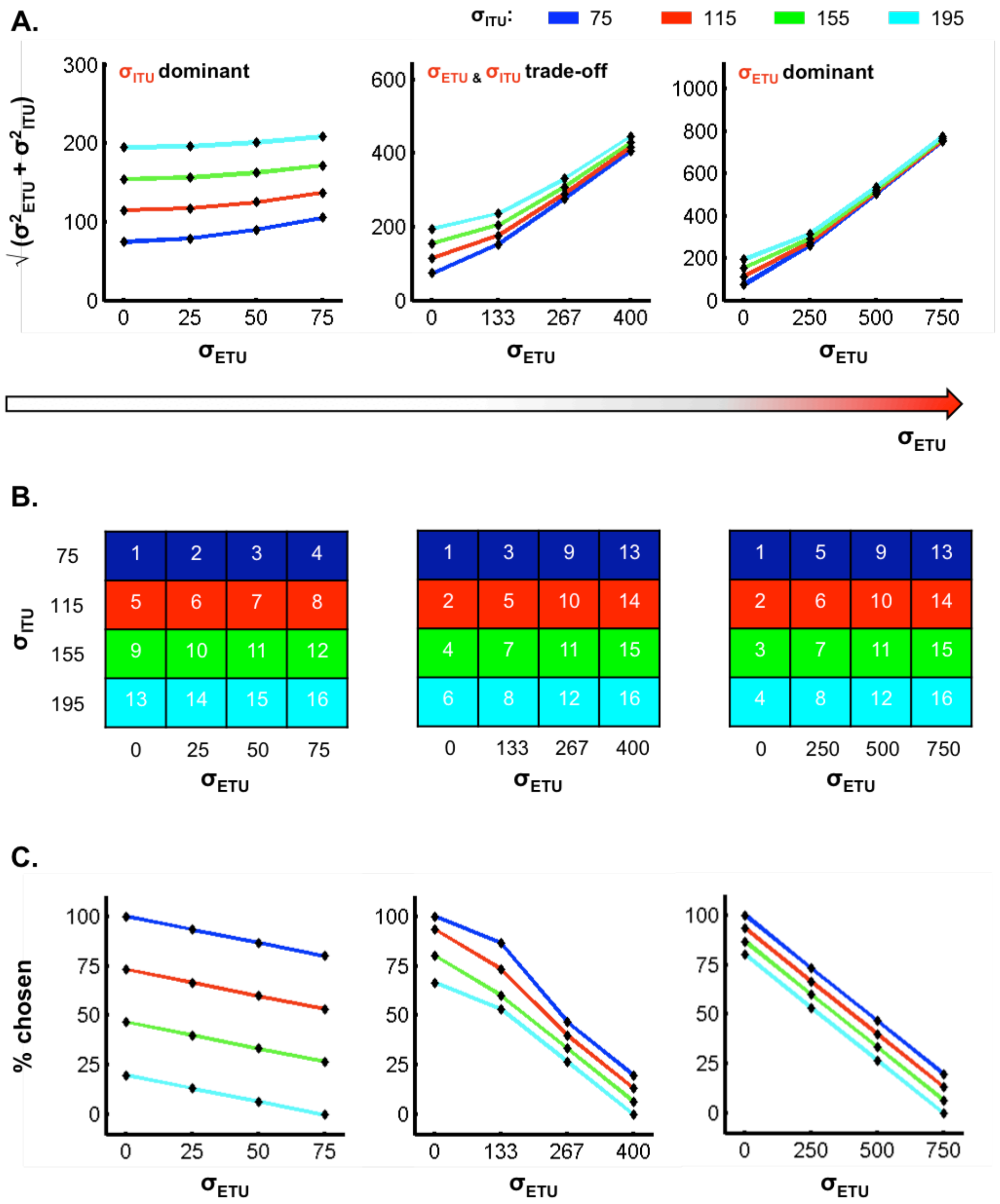


Figure 6.1: Indifference contours, optimal rank order, and optimal choice for 3 different scenarios. A. shows indifference contours for 16 combinations of ETU and ITU in three different scenarios (left, middle, right). On the left, the world is stable and ETU is low. Consequently, the contribution of ITU towards overall temporal uncertainty is large compared to the contribution of ETU. As such, ITU is dominant. Participants should *always* choose the combinations low in ITU. ETU is secondary. On the right, the word is unstable and ETU is high. The contribution of ETU towards temporal uncertainty is large compared to the contribution of ITU. ETU is dominant, participants should *always* prefer the combination low in ETU. ITU is secondary. In the middle, participants need to assess both ETU and ITU and trade-off ETU and ITU in choice. **B.** shows the optimal rank order based on the overall temporal uncertainty associated with each combination of ETU and ITU for each scenario (i.e. dominance) and **C.** depicts optimal choice.

Prior to the choice task, participants completed a large number of time interval reproduction trials, without preceding choice, and were given trial-by-trial feedback. This provided them with the opportunity to observe the effects of ETU and ITU on reward. Further, it allowed us to verify that ITU is indeed a random Gaussian variable and to compute predicted optimal choice behaviour.

We predicted that participants could form stable estimates of ETU and ITU and combine these estimates in choice. In line with previously reported optimal choice on motor-decision tasks, we expected accurate estimates of ITU. Three hypotheses were conceivable with regard to ETU: (i) in line with previous findings on decisions from *description*, participants may overweight small (and correspondingly underweight high) ETU; (ii) in line with previous findings on decisions from *experience*, participants may underweight small (and correspondingly overweight high) ETU; (iii) participants may form accurate estimates of ETU. If the latter hypothesis turned out to be true, then internal and external uncertainty would affect choice in much the same way; the *source* or *origin* of uncertainty would not matter for choice behaviour.

Method

Participants

Fifteen right-handed participants (3 male, mean age: 23 years, age range: 19 – 33 years) with normal or corrected-to-normal vision took part in this study, which was conducted with local ethics approval in line with the declaration of Helsinki. All participants gave written informed consent before participation.

Experimental procedure and design

An extensive training, which provided participants with the opportunity to learn ETU and ITU, was followed by a reward-based decision making task. In addition, before taking part in the experiment, participants completed a short pre-screen probing for existing biases in time interval reproduction.

Pre-screen for systematic biases in time interval estimation

Participants completed a time interval reproduction task with a ready-set-go procedure (Jazayeri & Shadlen, 2010). They were instructed to reproduce one out of four target intervals (TI: 750, 1150, 1550, 1950ms) on separate blocks. Participants received feedback about their mean reproduced TI, following completion of 10 trials, averaged across those 10 trials. Participants were excluded from further participation if their mean reproduced TI deviated more than 150ms from the corresponding TI (i.e. duration of the rewarded interval divided by two, see below) after 50 training trials (i.e. 5 sets of 10 trials each) for each of the four TIs. This pre-screen was aimed at reducing existing biases in time interval reproduction, and excluding participants if bias persisted, whilst providing limited information about trial-by-trial variability.

ETU and ITU Training

During the ETU and ITU training, participants completed the same time interval reproduction task as during pre-screen (see Figure 2A): they were instructed to accurately reproduce one out of four TIs (750, 1150, 1550, 1950ms). The timing of their response determined whether participants received positive feedback (see Figure 6.2B). Positive feedback depended on whether participants’ response fell inside a rewarded interval (RI) of 300ms. The mid-point of the RI was sampled from a Gaussian distribution, see Figure 6.2B. The TI set the mean of the Gaussian. The standard deviation of the Gaussian was set at one out of four values (0, 133, 267, 400ms). A higher standard deviation increases the variability of the RI and decreases the probability of reward. As such, the mean of the Gaussian manipulated ITU, due to the increase in ITU for longer TIs, while the standard deviation manipulated ETU.

There were 16 (= 4 x 4) possible combinations of the four levels of ITU and ETU. During training, participants were exposed to only seven of them, see Figure 6.2C. They experienced all four levels of ITU at lowest ETU, and all four levels of ETU at lowest ITU, to learn how ITU and ETU affect the probability of reward without concomitant changes in ETU and ITU, respectively.

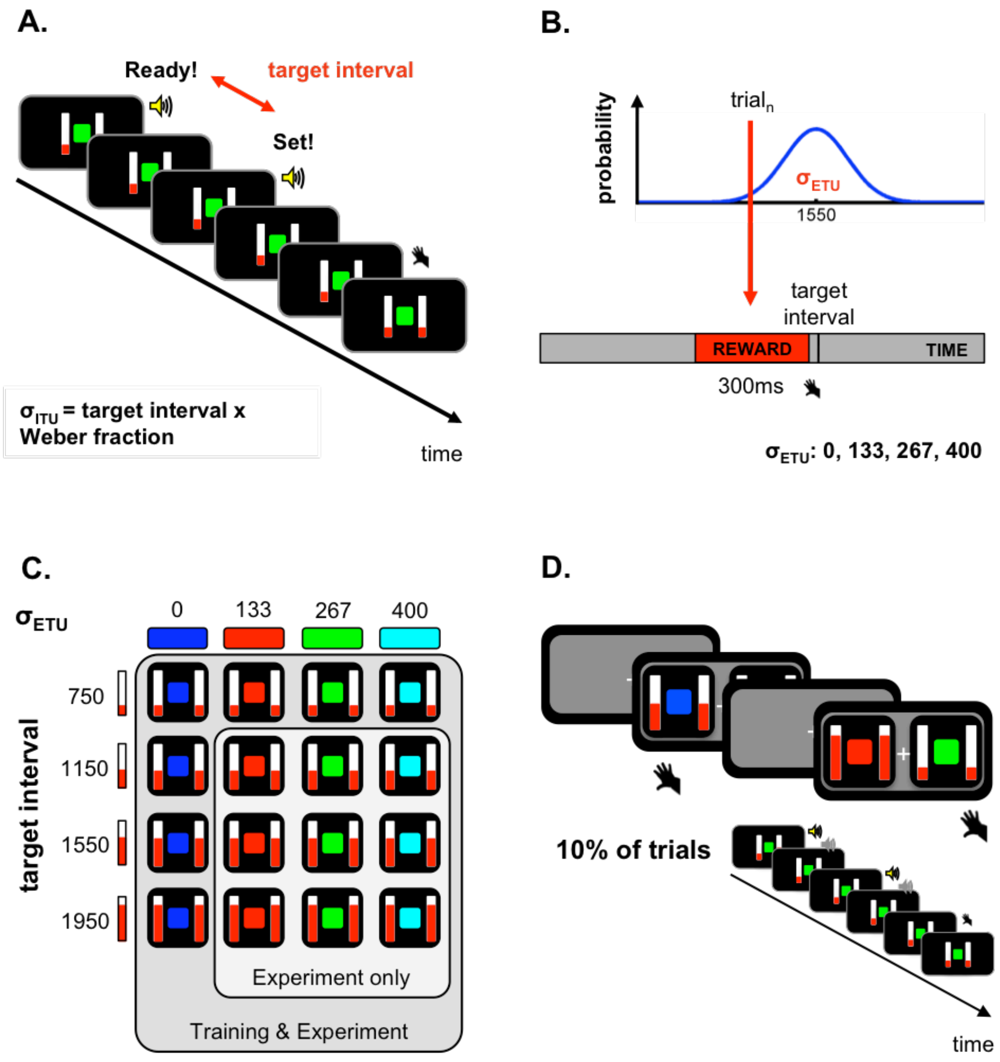


Figure 6.2: **Experimental design. A.** illustrates the ETU and ITU training. Participants performed an interval reproduction task with a ready-set-go procedure. They were instructed to reproduce the four target intervals as accurately as possible. Participants received trial-by-trial feedback about performance. **B.** feedback was dependent on whether the participant's response fell inside a rewarded interval. The mid-point of the rewarded interval was sampled from a Gaussian. The Gaussian was centred on the target interval. ITU increased with increasing time interval duration. The standard deviation was set at one out of four values. Higher standard deviation increases the variability of reward timing, thus manipulating ETU, and decreasing expected reward. **C.** four levels of ETU (indicated by colour) and four levels of ITU (indicated by the timer bars) were included. Participants trained with seven of the 16 possible combinations of the four levels of ETU and ITU. During the experiment, participants encountered all 16 combinations. **D.** participants completed a reward-based decision making task. They chose between pairs of stimuli (previously trials). On 10% of all trials, randomly selected, participants performed the interval reproduction task as during ETU and ITU training with the chosen combination of ETU and ITU. If their response fell inside the rewarded interval, then participants earned $0.25.

During training, participants were seated in front of a touch screen (32'') and wore headphones. On each trial, participants saw a centrally presented coloured target square (5cm^2: orange, green, blue, yellow) and "timer-bars" to the left and right of the target square (see Figure 6.2A). The colour communicated the level of ETU. The timer-bars informed participants about TI duration. Trials were initiated by key press on a standard QWERTY keyboard. 500ms after trial initiation, two auditory stimuli (300Hz, 50ms) occurred (READY and SET) separated by one out of the four TIs (750, 1150, 1550, 1950ms). Participants had to reproduce the TI by touching the target square at the centre of the screen at the appropriate time after SET. ETU and ITU training comprised eight blocks of ten repetitions each for each combination of ETU and ITU, in random order (70 x 8 trials = 560 trials). It took about an hour to complete.

Reward-based decision-making task

During the reward-based decision task, participants had to choose between two possible time interval reproduction trials (see Figure 6.2D). More specifically, on each decision trial, participants were presented with two possible time interval reproduction trials varying in ETU, ITU, or both. We instructed participants to select the time interval reproduction trial with the combination of ETU and ITU that they preferred. Participants were told that they could win a monetary reward ($0.25) on 10% of randomly selected trials. On these trials, following choice, participants performed the chosen time interval reproduction trial with its associated levels of ETU and ITU. Participants earned a reward if their time interval estimate fell inside the RI. As during training, the mid-point of this RI was sampled from a Gaussian distribution. The TI set the mean of the Gaussian and the standard deviation of the Gaussian was set at one out of four values (0, 133, 267, 400ms). To maximise expected reward, participants should choose the option with overall lower temporal uncertainty.

Choice trials were initiated by key-press. 500ms after trial onset, participants were presented with the stimuli, two coloured target squares ($5cm^2$) equidistant from the centre of the screen towards the left and right respectively. Colour indicated the level of ETU (orange, green, blue, yellow) and “timer-bars” to the left and right of each target square the level of ITU. During the choice task, participants encountered all 16 combinations of ETU and ITU. By touching the respective target square, participants chose between all possible 120 pairs of these 16 combinations of ETU and ITU, one pair at a time (excluding choice between time interval reproduction trials with identical ETU and ITU). Participants completed 4 blocks of 240 trials, thus repeating each possible pair of time interval reproduction trials eight times.

Following an actual time interval reproduction task trial (on those 10% of randomly selected trials on which participants could earn a reward) subsequent decision trials started no earlier than 2925ms after trial onset to prevent temporal discounting (i.e. choosing options with short TIs to shorten the experiment). In other words, there was no other benefit to choosing trials with short TIs than low ITU. Summary feedback was provided every 25 actually executed time interval reproduction trials. Overall, this choice task took 1.5 hours.

As participants were exposed to only seven out of the 16 possible combinations of ETU and ITU during ETU and ITU training, they could not choose based on the previously experienced frequency of reward associated with each combination of ETU and ITU during the main part of the experiment. Instead, participants had to use their individual estimates of ITU and ETU for choice particularly when choosing between novel environments.

Data analysis

ETU and ITU training

Reproduced TIs were computed as the time interval in between the second auditory stimulus (SET) and the participants' response. They were analysed with regard to mean accuracy (i.e. bias) and trial-by-trial accuracy, that is, variability across trials. To detect biases in time interval reproduction, the *actual* TI duration was subtracted from the mean *reproduced* TI duration. Difference scores were tested against zero using eight one-sample t-tests, one for each level of ETU (target interval: 750 ms) and one for each level of ITU (target interval: 750, 1150 1550 1950 ms). There should be no significant bias in time interval reproduction (in particular after having passed the pre-screen). Statistical threshold was thus set at alpha = 0.05 but *not* corrected for multiple comparison as such correction would have been to our advantage.

Standard deviation was analysed by fitting linear regression models to the standard deviation in reproduced TI against the level of ETU or actual TI duration for ETU and ITU, respectively. Regression coefficients were then tested against zero using one-sample t-tests. A positive slope would show an increase in standard deviation with increasing ETU or actual TI duration. The latter was expected (Gibbon, 1977; John Gibbon & Allan, 1984; Lejeune & Wearden, 2006) and would allow us to verify that ITU does indeed increase with longer TIs. ETU, by contrast, should not affect the standard deviation in reproduced TIs. But participants might react to increased variability in the RI (high ETU) by increasing the variability in their responses in the attempt to try to "chase up" the RI. To exclude this possibility, we tested for such potential change in the variability with levels of ETU.

Finally, the percentage of obtained reward was analysed by fitting linear regression models $y(x) = bx + a$ to the percentage of obtained reward against ETU or TI duration. Regression coefficients were extracted and tested against zero using one-sample t-tests. A negative slope would reveal a decrease in the percentage of obtained reward with increasing ETU and ITU, respectively, which was expected. As such, these tests revealed whether our manipulations of ETU and ITU were indeed effective.

Reward-based decision-making task

The number of times that a particular combination of ETU and ITU was chosen was indicative about participants' relative preference for all 16 combinations of ETU and ITU. We thus counted the number of times each combination was chosen by the participant during the experiment. We then determined whether ETU and / or ITU had any effect on participants' choice by computing a 4 x 4 within-subject repeated-measures ANOVA on preference. Subsequently, observed behaviour was compared to predicted optimal performance. Optimal performance was computed for each participant separately, to account for differences in ITU, following Equation (6.1):

$$\sigma_{TU} = \sqrt{\sigma_{ITU}^2 + \sigma_{ETU}^2} \tag{6.1}$$

σ_{TU}, σ_{ETU}, and σ_{ITU} refer to the level of overall temporal uncertainty, ETU, and ITU, respectively. ETU was set by the experimenter, and ITU by participants' accuracy in time perception measured during ETU and ITU training. We calculated the number of times that a given combination of ETU and ITU *should* have been chosen (i.e. optimal performance) separately for each participant. We then subtracted optimal from observed performance to test for *deviation* from optimal performance: negative values mean that a combination of ETU and ITU was chosen less often that it should have been and vice versa for positive values. First, to test for mere presence of bias, difference scores were tested against zero for all four levels of ETU (collapsed across ITU) and for all four levels of ITU (collapsed across ETU). Then, to detect differences in bias between the different *levels* of ETU and / or ITU, and a possible interaction in bias between ETU and ITU, we analysed difference scores (% observed - % optimal) with a 4 x 4 within-subject repeated-measures ANOVA with ETU and ITU as factors. Significant effects were followed up by paired t-tests corrected for multiple comparisons using Bonferroni correction. Greenhouse-Geisser correction was applied to degrees of freedom when sphericity assumptions were violated (Mauchly's test).

Results

Four participants were excluded after the pre-screen; eleven participants were entered into the analysis.

ETU and ITU training

Participants showed no systematic bias in time interval reproduction for low (ETU_0: $t_{(10)} = -0.39$, $p = 0.704$), low intermediate (ETU_{133}: $t_{(10)} = -0.18$, $p = 0.862$), high intermediate (ETU_{267}: $t_{(10)} = -0.18$, $p = 0.865$), and high ETU (ETU_{400}: $t_{(10)} = -0.75$, $p = 0.470$). There was no significant change in standard deviation in reproduced TIs with increasing ETU ($t_{(10)} = 0.72$, $p = 0.489$). The percentage of obtained reward decreased with increasing ETU ($t_{(10)} = -18.44$, $p < 0.001$; see Figure 6.3).

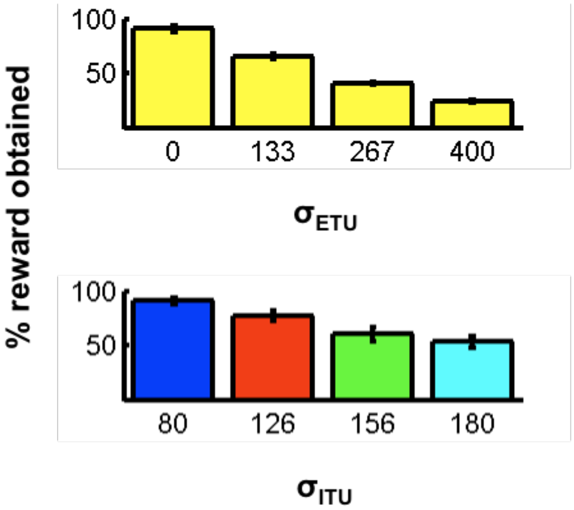


Figure 6.3: Percentage of reward obtained during ETU and ITU training. Reward decreased with increasing ETU due to higher variability in reward timing. Reward also decreased with increasing ITU due to higher variability in reproduced target intervals (TI) with longer to-be-reproduced TIs. Manipulations of ETU and ITU were thus successful.

Similarly, participants showed no systematic bias in time interval reproduction for short (TI_{750}: $t_{(10)} = -0.39$, $p = 0.704$), short intermediate (TI_{1150}: $t_{(10)} = 0.74$, $p = 0.479$), long intermediate (TI_{1550}: $t_{(10)} = -1.55$, $p = 0.153$), and long TIs (TI_{1950}: $t_{(10)} = -1.14$, $p = 0.281$). The standard deviation in reproduced TIs increased with increasing TI duration ($t_{(10)} = 6.93$, $p < 0.001$), which verified that ITU did indeed increase with increasing TI duration (Weber property). Consequently, the percentage of obtained reward decreased with increasing TI duration / ITU ($t_{(10)} = -7.58$, $p < 0.001$; see Figure 6.3).

Taken together, we found no evidence for bias in time interval reproduction for the four levels of ETU and ITU. Standard deviation in reproduced TIs increased with increasing TI duration, which confirms that ITU increases with increasing TI duration, while the standard deviation did not change for varying ETU. Finally, participants experienced changes in the probability of reward as a consequence of varying ETU or ITU. Our experimental manipulations were thus successful.

Reward-based decision-making task

ETU and ITU contributed independently towards participant's choice ($F_{(2.60, 25.96)} = 2.01, p = 0.132, \eta_p^2 = 0.173$; see Figure 4). Choice was affected by ITU ($F_{(1.14, 25.96)} = 26.58, p < 0.001, \eta_p^2 = 0.727$). Collapsed across ETU, preference decreased with increasing levels of ITU (ITU_{750} vs. ITU_{1150}: $t_{(10)} = 4.15, p < 0.0167$; ITU_{1150} vs. ITU_{1550}: $t_{(10)} = 6.31, p < 0.0167$; ITU_{1550} vs. ITU_{1950}: $t_{(10)} = 4.02, p < 0.0167$; see Figure 6.4). Similarly, ETU had a significant effect on participants' preference ($F_{(1.37,25.97)} = 8.72, p = 0.007, \eta_p^2 = 0.466$) Collapsed across ITU, participants avoided the highest level (ETU_{267} vs. ETU_{400}: $t_{(10)} = 3.36, p < 0.0167$). The data revealed a trend towards preferring the lowest level of ETU (ETU_0 vs. ETU_{133}: $t_{(10)} = 2.75, p = 0.021$). By contrast, participants showed indifference towards the two intermediate levels of ETU (ETU_{133} vs. ETU_{267}: $t_{(10)} = 0.59, p = 0.569$; Figure 3). Taken together, participants' behaviour was guided by a decrease in reward probability with increasing ITU and ETU except for an indifference towards the two intermediate levels of ETU. ETU and ITU had a clear effect on participants' choice (see Figure 6.4).

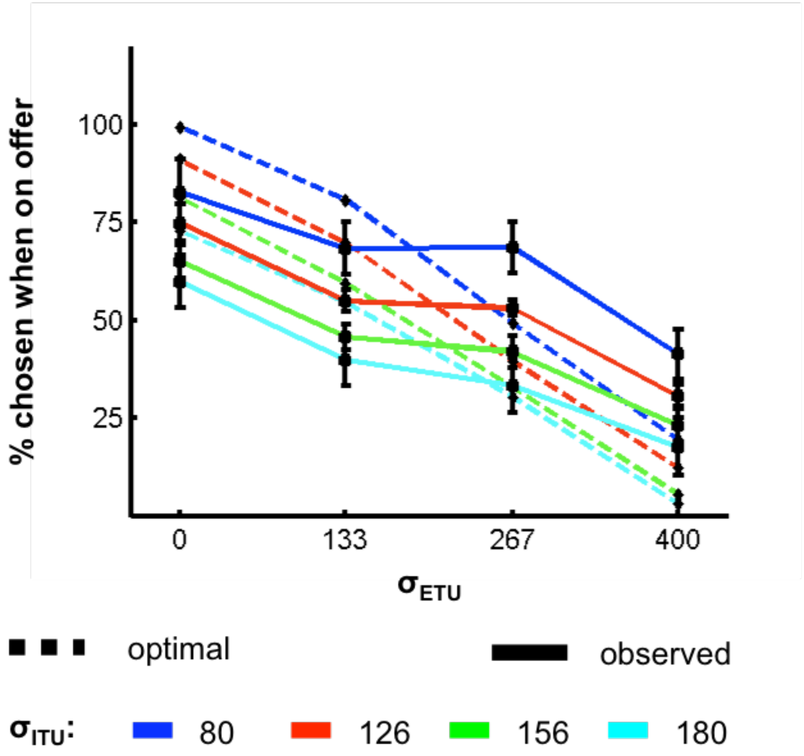
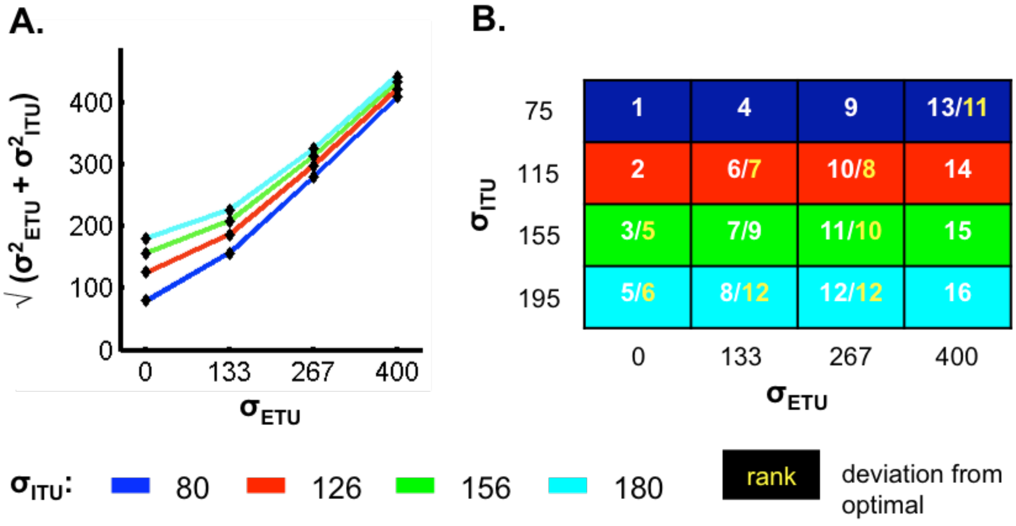


Figure 6.4: Choice behaviour on the reward-based decision making task. Participants' preference decreased progressively with increasing ITU. Participants avoided high and preferred low ETU. They were indifferent towards intermediate values of ETU. Comparison between bold (observed) and dashed (optimal) lines reveals that observed deviates from optimal performance.

The four levels of ETU, as experimentally manipulated, and estimates of the four levels of ITU, extracted from participants' training data, allowed us to compute indifference contours for all 16 combinations of ETU and ITU, see Figure 6.5A, as well as to predict optimal performance following Equation 6.1. Observed behaviour differed from optimal performance, see Figure 6.5B. In select cases, participants preferred combinations of ETU and ITU with overall higher temporal uncertainty (e.g. low ITU and high intermediate ETU) over combinations of ETU and ITU with overall lower temporal uncertainty (e.g. high intermediate ITU and low intermediate ETU; see Figure 6.5B).



σ_{ITU} \ σ_{ETU}	0	133	267	400
75	1	4	9	13/11
115	2	6/7	10/8	14
155	3/5	7/9	11/10	15
195	5/6	8/12	12/12	16

Figure 6.5: Indifference contours, optimal and observed rank order. Indifference contour **A.** and optimal versus observed rank order **B.** modelled on experimentally manipulated ETU and ITU extracted from ETU and ITU training data for each participant separately. The observed rank order differs from the optimal rank order (values in yellow). In selected cases, combinations of ETU and ITU with associated higher temporal uncertainty (e.g. high intermediate ETU and low ITU) were preferred over stimuli with associated lower temporal uncertainty (e.g. low intermediate ETU and high intermediate ITU). Comparison of A. with Figure 6.1A illustrates that neither ETU nor ITU should strongly dominate participants' choice.

The analysis of the difference scores (% observed choice - % optimal choice) revealed that deviation from optimal performance was driven primarily by biased estimates of ETU (see Figure 6.6). Collapsed across ITU, participants were biased in their estimates of low intermediate ETU ($t_{(10)}$ = -7.52, $p < 0.001$) and high intermediate ETU ($t_{(10)}$ = 3.50, p = 0.023). The data furthermore revealed a trend towards a biased estimate for high ETU ($t_{(10)}$ = 2.87, p = 0.067). These biases were different for the four levels of ETU ($F_{(1.29,12.91)}$ = 8.35, p = 0.009, η_p^2 = *0.455).* Bias was comparable for low and low intermediate ETU ($t_{(10)}$ = -0.24, p = 0.815) and high intermediate and high ETU ($t_{(10)}$ = -1.13, p = 0.284). However, whilst participants overestimated low and low intermediate ETU, they underestimated high intermediate and high ETU (ETU_{133} vs. ETU_{267}: $t_{(10)}$ = -5.49, $p < 0.001$). A positive regression coefficient (mean = 0.095, SE = 0.032), extracted from a linear regression model fitted to the difference scores against ETU for each participant separately, confirmed this trend from over- to underestimation with increasing ETU ($t_{(10)} = 2.97$, p = 0.014). As ETU increases, a significant overestimation turns into an underestimation of ETU.

In contrast, we found no bias in the estimates of ITU (all p > 0.1) and no difference in bias between the estimates of the four levels of ITU ($F_{(3,30)} = 0.60$, p = 0.623, η_p^2 = *0.056).* Similarly, regression coefficients, extracted from a linear regression model fitted to the difference scores against level of ITU computed for each participant separately, did not differ from zero (mean = -0.0044, SE = 0.0046; $t_{(10)} = -0.96$, p = 0.358).

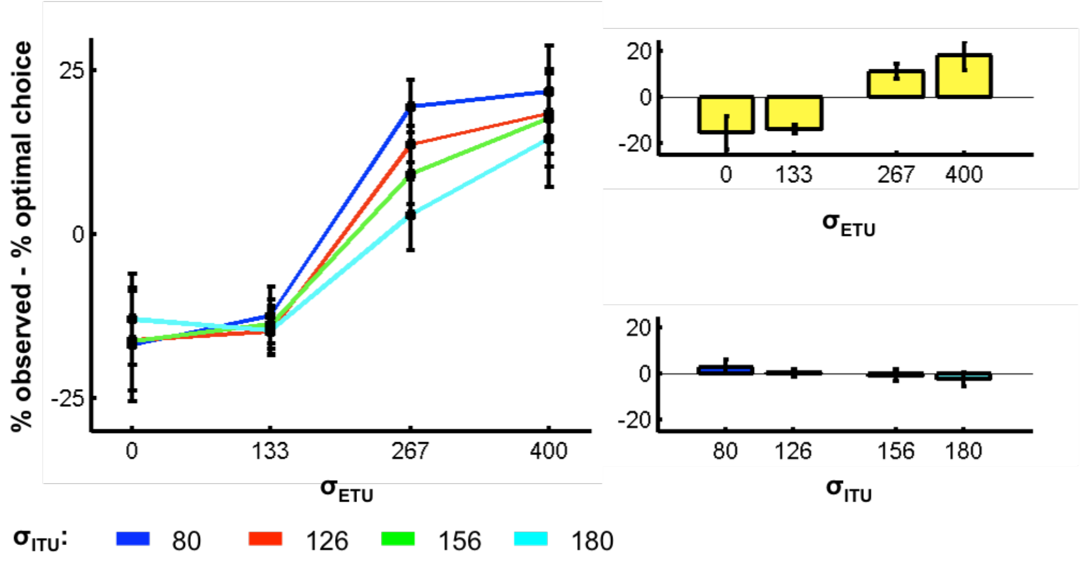


Figure 6.6: Deviation from optimal performance in choice. Observed behaviour differed from optimal performance. This deviation was largely due to biased estimates of ETU (top right). Participants overestimated low intermediate ETU and underestimated high intermediate ETU. Estimates of ITU showed no such bias (bottom right). In addition, the underestimation of high intermediate ETU was more pronounced for low versus high ITU. A similar pattern was found for high ETU albeit not significant (left).

Finally, we found a significant interaction between ETU and ITU ($F_{(3.71,\,37.11)} = 3.62$, p = 0.016, η_p^2 = *0.266).* Post-hoc t-tests revealed a more pronounced underestimation of high intermediate ETU at low versus high ITU ($t_{(10)} = -2.39$, p = 0.074). The data reveal a similar though not significant pattern for high ETU ($t_{(10)} = -2.06$, p = 0.13).

Taken together, while ETU and ITU influence participants' choice, observed choice differs from predicted optimal performance. This difference was primarily caused by biased estimates of ETU but not ITU. Estimates of high intermediate ETU may depend on the level of ITU.

Discussion

At the moment of choice the outcome of actions is uncertain. This uncertainty is partly due to variability in the outside world (i.e. externally generated variability, here ETU) and partly due to sensorimotor noise (i.e. internally generated variability, here ITU). We assessed, using a novel experimental paradigm, whether participants can accurately estimate and combine external (ETU) and internal temporal uncertainty (ITU) in a reward-based decision making task that puts a premium on accurate action timing.

ETU and ITU contributed independently towards participants' choice. Choice decreased consistently with increasing ITU. Participants avoided the highest and preferred the lowest level of ETU but they were indifferent towards intermediate values. Thus, participants formed stable and independent estimates of both ITU and ETU during training, except for intermediate values of ETU. In choice, they combined these estimates to select one combination of ETU and ITU above another. These results demonstrate that the ETU and ITU training was effective. The paradigm presented in this study thus allows, for the first time, to study decision making under both external and internal temporal uncertainty. Second, it suggests that participants are better at forming reliable estimates of ITU compared to estimates of ETU.

Optimal performance was modelled based on observed ITU (i.e. trial-by-trial accuracy in reproduced TIs) and experimentally manipulated ETU. Observed behaviour differed from optimal performance. In selected cases, participants preferred options with comparatively high temporal uncertainty above options with comparatively low temporal uncertainty. In other words, participants preferred options with lower expected reward above options with higher expected reward. This sub-optimal performance was largely due to biased estimates of ETU. Low values of ETU were overestimated. In other words, participants erroneously believed that options associated with low ETU were less good than they actually were. Conversely, participants underestimated high values of ETU: participants thought that options associated with high ETU were better than they actually were. In contrast, we observed no such biases for ITU. However, we found a small but significant interaction between biases in estimates of ETU and ITU. We found a trend towards a marginally more pronounced bias for high intermediate ETU for low versus high ITU. We found a comparable pattern for high ETU albeit not significant.

Importance of the origin of uncertainty

The data reveal that the origin of temporal uncertainty matters for choice. While participants can form accurate estimates of ITU (cf. Gepshtein et al., 2007; Trommershäuser et al., 2005, 2006), their estimates of ETU are biased (cf. Kahneman & Tversky, 1979; Tversky & Kahneman, 1992). Consequently, choice under conditions of ETU will be sub-optimal while performance will approach optimality under conditions of ITU. We suggest two alternative explanations for biased estimates of ETU. First, biases might reflect a strategic response towards uncertainty *about* the estimates of ETU (Jazayeri & Shadlen, 2010) but not ITU. Second, biases might be due to distortion of small probabilities (Kahneman & Tversky, 1979; Tversky & Kahneman, 1992) for ETU but not ITU.

Uncertainty about ETU estimates

Participants may have experienced uncertainty *about* their estimates of ETU. This uncertainty may have caused a “regression towards the mean”, here expressed by an overestimation of low and an underestimation of high ETU. This regression towards the mean may constitute a strategic response towards the experienced uncertainty about ETU estimates. In a recent study, Jazayeri and Shadlen showed that regression towards the mean reflects prior expectation. They instructed participants to estimate time intervals in a ready-set-go procedure (Jazayeri & Shadlen, 2010). Participants systematically overestimated time intervals shorter than and underestimated time intervals longer than the mean target interval duration. Importantly, the degree of over- or underestimation was modulated by the temporal uncertainty that participants experienced regarding the true duration of the time interval that they were supposed to judge. Longer time intervals, associated with a higher level of ITU, were biased more strongly towards the mean than shorter time intervals. In other words, the influence of prior expectation grows with increasing uncertainty.

Similarly, the overestimation of high and the underestimation of low ETU might reflect the influence of prior expectation established across trials (i.e. the mean of the four values of ETU). The indifference towards intermediate values of ETU might be a consequence of this influence of prior expectation. As estimates are regressed towards the mean, differences close to the mean decrease and may become too small to be detected by statistical tests.

Interestingly, we did not find the same bias for estimates of ITU. Participants’ estimates of ITU are highly accurate (contrary to Mamassian, 2008), which may be due to a lifetime’s experience with one’s internally generated temporal uncertainty. Alternatively (or, in addition), the way participants learn about ITU might be superior to how it is that participants learn about ETU. Learning ETU is entirely dependent on feedback. In the present study, feedback was binary: either participants received the reward or they did not. If participants did not receive the reward, then they had no means of telling how far off they were from the rewarded time interval (or indeed, how well they performed). In contrast, re-afferent information may provide participants with a better ‘error signal’. By comparing the efference copy (a prediction of re-afferent information generated during action selection and execution: Flanders, 2011; Körding & Wolpert, 2004) with ensuing re-afferent information, participants might be able to estimate how far off they were in reproducing the target interval. This quantitative information might allow them to form more reliable and highly accurate estimates of ITU. But how does the brain access this information and how does it integrate the efference copy with feedback about reward? Answers to these questions have to await further studies. Importantly, the results point towards a clear difference between ETU and ITU, based on their origin and suggests a fundamental advantage of ITU.

Distortion of small probabilities

Alternatively, the bias in the estimates of ETU may be due to the distortion of small probabilities (Kahneman & Tversky, 1979; Kahneman & Tversky, 2000; Tversky & Kahneman, 1992). Participants are known to overestimate small probabilities, which is why we buy lottery tickets. Such overestimation may have caused stronger preference compared to optimal performance for options associated with high temporal uncertainty (low probability of reward). Conversely, options associated with low temporal uncertainty (high probability of reward) were chosen less often.

Crucially, we do not find such bias for estimates of ITU. This suggests that distortion of probabilities happens for externally but not internally generated uncertainty. Again, these results reveal a fundamental difference between ETU and ITU and suggests that the origin of uncertainty, rather than how participants learn about uncertainty, determines whether or not participants show patterned deviations from optimality.

We speculate that these two alternative explanations for the observed biases in estimates of ETU are not exclusive. The distortion of small probabilities may be due to a regression towards the mean. Effectively, “distortion of small probabilities” describes a data-pattern that has been found previously. “Regression towards the mean” may explain why it is that participants distort small probabilities in the first place: participants may have experienced uncertainty *about* their estimates (here, ETU only).

Conclusions

This study introduces a novel paradigm to study the contribution of internally (ITU) and externally (ETU) generated temporal uncertainty towards choice in a reward-based decision task. Participants’ choices were guided by ETU and ITU but observed performance differed from predicted optimal performance. This deviation was driven primarily by biased estimates of ETU. We suggest that biased estimates of ETU reflect higher uncertainty about parameter estimates. This uncertainty leads to a “regression towards the mean” expressed as distortion of small probabilities. We did not find any such biases for ITU, although participants learned about both ETU and ITU by extensive sampling (i.e. experience). This study thus reveals a fundamental difference between ETU and ITU in choice. The *origin* of noise determines its effects on reward-based choice.

Chapter 7: Temporal cue integration to reduce internal temporal uncertainty

Abstract: Time is a ubiquitous aspect of perception, cognition, and action but time perception is inaccurate. Temporal noise increases with the duration of time-intervals to-be-judged, and induces internal temporal uncertainty (ITU) about the timing of events or actions, with detrimental effects on performance. Combining information from multiple sources reduces sensory and motor noise which benefits performance. We asked whether participants can combine temporal information from multiple cues to reduce ITU. Participants reproduced a time-interval in a READY-SET-GO procedure. An additional temporal stimulus (AS) occurred at a fixed time *before* the correct time to respond, but *after* SET. Combining temporal information provided by both SET and AS should lead to more accurate time-interval reproduction than relying on either cue alone. Analysis of participants' variability in time-interval reproduction did not show this improvement. Instead, participants relied on the more accurate cue (AS) to time their responses. Cue integration may require not only correlated percepts but correlation with temporal proximity, which suggests that cue combination is no general-purpose mechanism for sensory-motor noise reduction. Rather, it features in the inference from sensory percepts to common but hidden causes. The constraint of temporal proximity may aid us in correctly inferring the cause of sensory signals at the expense of timing accuracy.

Keywords: cue integration, cue combination, timing, time interval reproduction, uncertainty, internal temporal uncertainty

Motor performance often depends on the accurate perception of time (J. Coull & Nobre, 2008; Nobre et al., 2007). But accuracy in time perception is limited: “internal clocks” are noisy. We experience ITU about behaviourally relevant events, or appropriate timing for motor action (Gibbon, 1977; Gibbon & Allan, 1984; Lejeune & Wearden, 2006; Lewis & Miall, 2009). In this chapter we explore first, whether participants are able to extract temporal information from multiple temporal cues, and second, whether participants can combine this information to reduce ITU to improve performance. To date, this is the first study, as far as we know, on the reduction of internally generated temporal uncertainty (ITU) by temporal cue integration.

There are many examples of successful cue integration in the literature. (Ernst & Banks, 2002; Girshick & Banks, 2009; Hillis, Ernst, Banks, & Landy, 2002; Hillis, Watt, Landy, & Banks, 2004; Johnston, Cumming, & Landy, 1994; Knill, 2007; Knill & Saunders, 2003). Localization of one's own limbs (Sober & Sabes, 2005; van Beers, Wolpert, et al., 2002), or entire body (Fetsch et al., 2010, 2009) improves through the integration of visual and proprioceptive information. Finally, motor performance improves through the integration of visual and proprioceptive information with the efference copy, a prediction about the sensorimotor consequences of motor actions (Bays & Wolpert, 2007; van Beers, Baraduc, et al., 2002; Wolpert, 2007).

We can compute the maximum possible improvement in performance as a result of the *optimal* integration of two separate cues in the following way: assume that these cues are independent Gaussian random variables $S_i, i = 1,2$ that signal a common property $s = E[S_i]$. The cues have variances $\sigma_i^2, i = 1,2$ respectively. The maximum possible improvement in mean performance as a result of optimal cue integration is computed using Equation 1 by linearly combining the two cues into a single estimate (Oruç, Maloney, & Landy, 2003):

$$S = w_1 S_1 + w_2 S_2 \tag{1}$$

with $w_1 + w_2 = 1$ and

$$w_i = \frac{\sigma_i^{-2}}{\sigma_1^{-2} + \sigma_2^{-2}} \tag{2}$$

The resulting estimate S is an unbiased estimate, $E[S_i] = s$, and, among unbiased estimates, it has the minimum variance (Oruç et al., 2003). The variance of the resulting estimate is:

$$Var[S] = \sigma^2 = \frac{\sigma_1^2 \sigma_2^2}{\sigma_1^2 + \sigma_2^2} \tag{3}$$

and it can be shown that the estimate S has lower variance than either cue alone (Oruc et al, 2003). We will typically make use of the standard deviation rather than the variance in comparing observed performance to optimal:

$$\sigma = \sqrt{\frac{\sigma_1^2 \sigma_2^2}{\sigma_1^2 + \sigma_2^2}} \tag{4}$$

In many tasks, participants integrate the information provided by multiple cues to achieve an observed accuracy in their final estimate that is close to the maximum possible (Ernst, 2007; Ernst & Banks, 2002; van Beers, Baraduc, et al., 2002). Recently, two studies have reported a close to optimal improvement in performance on an implicit timing task (i.e. a finger tapping task) due to integration of sensory information (Elliott, Wing, & Welchman, 2010; Wing, Doumas, & Welchman, 2010). In a unimodal condition, participants synchronised finger tapping with auditory, visual, or tactile events. In a bimodal condition, participants synchronised finger tapping with pairs of events taken from two different modalities presented either simultaneously or with a slight off-set. Variability in timing error (i.e. the variability in the asynchrony between stimulus presentation and the finger tap) decreased in the bimodal versus the unimodal condition as predicted by Equation 3. Cue integration can thus improve accuracy on an implicit timing task.

Elliott et al., however, did not address whether cue integration can reduce internal temporal uncertainty (ITU). Rather, they assessed whether having better information about the timing of events (i.e. in the bimodal condition as the result of cue integration) increases the ability to synchronize movement with these events. In other words, they investigated the beneficial effects of reduced sensory uncertainty about the timing of sensory events in the bimodal condition (i.e. *when* these events happened) on rhythmic movements synchronised with these sensory events. By contrast, in the current study, we were specifically interested in cue integration in the temporal domain as a means to reduce ITU (i.e. the temporal uncertainty associated with the *passage* of time): can participants extract and integrate temporal information from multiple temporal cues to improve their accuracy in time perception?

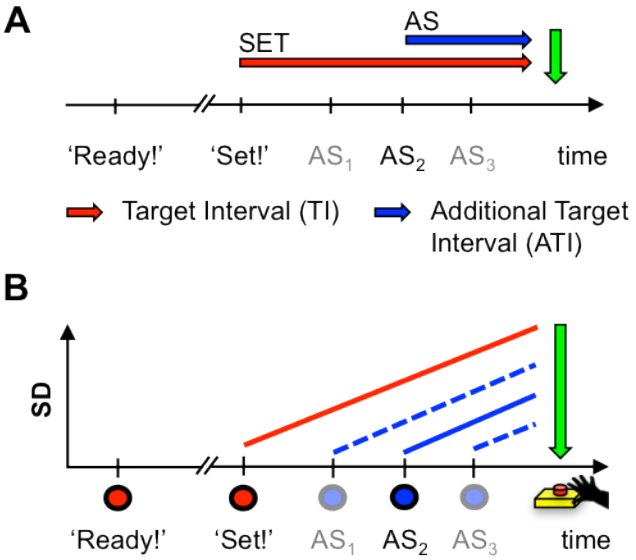


Figure 7.1: Schematic illustration of experimental design. A SET instructs participants to respond once the target interval (TI) has passed and thus acts as a cue for the timing of future action. The additional stimulus (AS) provides additional temporal information about when to respond as it occurs at a fixed time interval before the correct time to respond. **B** Relation between the timing of SET, the additional stimulus (AS), and internal temporal uncertainty (ITU). Variability in time interval reproduction σ_R increases with increasing time interval duration. Because SET occurs before the AS, ITU associated with the additional target interval (ATI) is lower at the time of action compared to the ITU associated with the target interval (TI). The specific level of ITU associated with the ATI depends on the timing of the AS. Participants may use information provided by the AS and SET in conjunction to time future action. Alternatively, participants may use the SET or the AS only.

Participants completed a time interval reproduction task with a ready-set-go procedure (Jazayeri & Shadlen, 2010). They were instructed to estimate and reproduce a time interval in between a READY and a SET cue (i.e. the target interval (TI) of 2262ms). After SET, participants received an additional stimulus (AS) at a fixed time interval before the correct time to respond.

Formally, such an AS provides additional temporal information about the timing of the required response. The level of temporal information provided by the AS depends on the time interval in between the AS and the required response (i.e. the additional target interval: ATI). The longer the ATI, the less additional temporal information is provided by the AS because of the scalar property of interval timing (Gibbon, 1977; Gibbon & Allan, 1984; Lejeune & Wearden, 2006; Lewis & Miall, 2009). We varied the level of temporal information provided by the AS by varying the ATI (412ms, 1037ms, or 1662ms) and assessed whether variability in time interval reproduction reduced in line with Equation 3. To compute predicted optimal performance for each participant individually, we measured variability in time interval reproduction for the TI and the three ATIs using a standard time interval reproduction task, again with a ready-set-go procedure, without the presentation of an AS. In other words, during this baseline, the ATI was presented like a regular target interval.

We considered three alternative hypotheses about how participants might carry out the task with the two cues, SET and AS. First, participants might ignore the AS and use only SET for timing their responses (***Hypothesis 1: SET only***). *Hypothesis 1* predicts a standard deviation in the response σ_R equal to the standard deviation for the TI (2262ms) as measured during baseline (i.e. without the AS) for all three experimental conditions (i.e. all three ATIs):

$$\sigma_R = \sigma_{TI} \tag{5}$$

Second, participants might integrate the temporal information provided by SET and the temporal information provided by the AS in the optimal fashion prescribed by Equations 1 and 2 (***Hypothesis 2: optimal integration***). The standard deviation in the response σ_R should thus equal:

$$\sigma_R = \sqrt{\frac{\sigma_{TI}^2 \sigma_{ATI}^2}{\sigma_{TI}^2 + \sigma_{ATI}^2}} \tag{6}$$

Further, the standard deviation σ_R should increase with increasing ATI duration due to an increase in σ_{ATI}. Third, participants might ignore the SET cue and use the temporal information provided by the AS cue only (***Hypothesis 3: AS only***). In this case, the duration of the ATI alone should determine the standard deviation in TI reproduction:

$$\sigma_R = \sigma_{ATI} \tag{7}$$

and the standard deviation σ_R should increase linearly with increasing ATI duration due to increasing σ_{ATI}. Both, Hypothesis 2 and 3 require that participants learn the ATI whereas Hypothesis 1 does not. To learn the ATI, participants have to first use SET to estimate the correct time for action to then estimate the ATI in between the correct time for action and the AS. Thus, being able to use the AS to improve performance entails that participants can use SET, but not vice versa. Thus, participants may use SET only, and ignore the AS, because they are unable to learn the ATI. If participants use the AS but ignore SET, then because they fail to integrate the information provided by the SET and the AS, although they can use both cues separately to time required responses. Finally, if participants integrate temporal information provided by the SET and the AS, then they are able to use the AS and the SET in conjunction for optimal improvement in timing accuracy.

Given reports of near-optimal cue integration in the visual and motor domain (Elliott et al., 2010; Ernst & Banks, 2002; Fetsch et al., 2010; Hillis et al., 2004; Knill, 2007; Muller, Brenner, & Smeets, 2009; Sober & Sabes, 2005; van Beers, Baraduc, et al., 2002; Wing et al., 2010), we expected near-optimal cue integration in the temporal domain.

Method

Participants

Six participants (mean age: 27.2 years, age range: 24 – 32 years, all right handed, three males, normal or corrected-to-normal vision) took part in this study after having provided written informed consent. They received compensation for their time and effort (£85). The study was approved by a local ethics committee and in line with the declaration of Helsinki.

Procedure

Participants were seated in front of a computer screen (approximately 60cm viewing distance) and wore noise-cancelling headphones to attenuate background noise and, in particular, the sound of participants pressing the response key. Their right index finger rested on the space-key of a standard QWERTY keyboard, which served as the response key.

Task & design

Participants completed a modified time interval reproduction task with a READY-SET-GO procedure (Jazayeri & Shadlen, 2010). Trial start was signalled by presentation of a small white ring (1.5 degree visual angle) on dark grey background. The ring was presented centrally and participants were instructed to fixate. 300ms after trial-onset, participants saw a small red circle (READY; 1.5 degree visual angle), briefly flashing at the centre of the screen (100ms), followed by a second red circle (SET; 1.5 degree visual angle; 100ms), separated by the target interval (TI: 2262ms). Participants were instructed to reproduce the TI by responding when the time interval after SET matched the time interval in between READY and SET. As such, SET acted as a cue for the timing of future action (Figure 7.1A).

Participants received the AS before the correct time to respond, a small blue circle (1.5 degree visual angle) briefly flashing at the centre of the screen (100ms). The AS marked the onset of the ATI (412ms, 1037ms, or 1662ms). The timing of the AS was manipulated in a block-wise fashion (i.e. within each block, SET and AS were perfectly correlated).

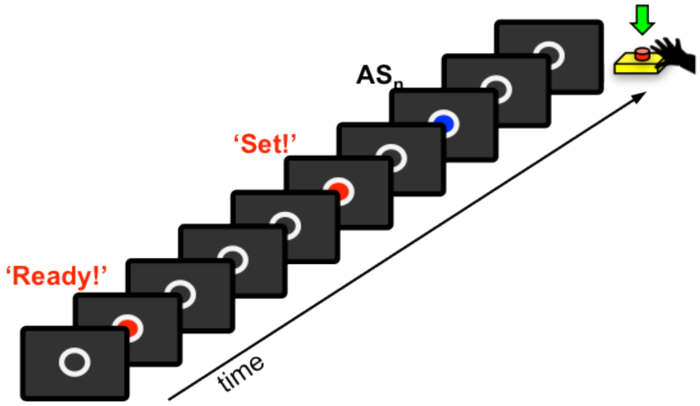


Figure 7.2: Experimental task. Modified time interval reproduction task with a READY-SET-GO procedure. Participants were instructed to respond when the time interval following SET matched the time interval in between READY and SET (2262ms). 412, 1037, or 1662ms before the end of the reference interval (GO), participants saw an additional stimulus (AS). The blue circle provided information about the right time for action, in addition to SET, as it occurred at a fixed time interval before the correct time to respond (i.e. the additional target interval: ATI).

Following the AS, the white ring disappeared after twice the TI (2 x 2262ms), as measured from SET. This long time interval ensured that participants could indicate their estimate of the TI even if they strongly overestimated the TI. In addition, the white ring stayed on for an additional time interval sampled from a truncated non-aging exponential distribution (lower bound = 200ms, mean = 500ms, upper bound = 800ms). This temporal jitter prevented participants from using the offset of the ring as a cue informative about the accuracy of their just provided TI estimate. The inter-trial interval was sampled from the same truncated non-ageing exponential distribution to prevent build-up of expectancy about trial onset.

Participants completed the experiment in three sessions (650 trials each = 2h), one for each ATI, separated by at least 24 hours. The order of experimental conditions (i.e. ATIs) was counterbalanced across participants. Summary feedback about average performance was given every 50 trials, and was informative about direction and magnitude of bias but not about trial-by-trial variability.

Each session was preceded by a short training session. First, participants completed 10 trials with trial-by-trial feedback to get used to the duration of the TI, followed by sets of 10 trials, each with summary feedback about performance upon completion of a set. Participants were allowed to proceed with the experiment once the mean of the reproduced TI did not deviate by more than 10% from the actual TI. This training was included to reduce existing biases in time perception (Lewis & Miall, 2009a). Overall, participants showed little bias in time interval perception (median # of required training blocks = 1.25).

Baseline performance in time interval reproduction

During baseline, participants completed the time interval reproduction task, as described above, with two modifications: participants did not receive the AS, and they reproduced four different target intervals in different blocks (the TI: 2262ms and all three ATI: 412ms, 1037ms, 1662ms).

Participants completed the baseline in two sessions. One session (4 blocks, one for each ATI and TI, of 150 trials each) took place before and the other after the experiment to capture any improvement in baseline performance due to completion of the experiment. The order of the blocks during baseline was randomised. Each block was preceded by 10 trials with trial-by-trial feedback and sets of 10 trials with summary feedback upon completion of a set. As before, participants showed little initial bias in time interval reproduction (median # of required training blocks = 1.25 for both pre- and post-experiment baseline).

Data analysis

We specifically asked about precision and mean accuracy in time interval reproduction after prolonged training and exposure to the AS. To this end, we analysed the final 200 trials participants completed in each experimental condition, in particular to ensure that participants were given the opportunity to learn a block's ATI across the 450 trials preceding these analysed 200 trials. Correspondingly, to ensure that participants were sufficiently familiar with the TI and ATIs during baseline, we analysed the final 100 trials participants completed for each time interval in both the pre- and post-experiment baseline session (i.e. 200 baseline trials analysed in total for each time interval).

Reproduced target interval duration was computed as the time interval in between SET (i.e. the centre of the 100ms visual stimulus) and participant's response. All reproduced target intervals < 0ms (i.e. responses before SET) were excluded from further analysis (Baseline: 0.2%; Experiment: < 0.1%). Outliers were identified using Grubb's test (α = 0.05) and excluded (Baseline: 0.7%; Experiment: 1.6%). We acknowledge that exclusion of outliers in reproduced TIs affects the standard deviation. However, this effect will be limited due to the small number of excluded trials. We then analysed the standard deviation in reproduced TIs, as a measure of precision, and the mean of reproduced TIs, as a measure of bias. Before we computed the standard deviation, across all trials for each experimental condition separately, we removed any slow drifts from the data (Helmuth & Ivry, 1996).

Removal of gradual changes in estimated target interval duration

Gradual changes in the mean of the reproduced target interval over time affect the observed standard deviation but such changes are not an expression of participants' "true variability" in time interval reproduction. Instead, they reflect slow drifts in the *mean* of the distribution of reproduced TIs. To get a better estimate of participants' variability, we first removed such slow drifts before we computed the standard deviation across trials.

Slow drifts were removed in two consecutive steps: first, we removed any linear trends from the data that suggest a linear in- or de-crease in the mean of reproduced TIs separately for each "mini-block" (i.e. 50 trials uninterrupted by feedback; 1st step). We fitted a linear regression model to the data (i.e. TI estimates) separately for each mini-block. We then used this linear model to remove linear trends by subtracting the variance accounted for by the regression from the raw TI estimates. With this procedure, we effectively computed the variance that was not accounted for by the regression (i.e. the residuals). As such, this procedure accounts for slow gradual changes in mean reproduced TIs on trials uninterrupted by feedback.

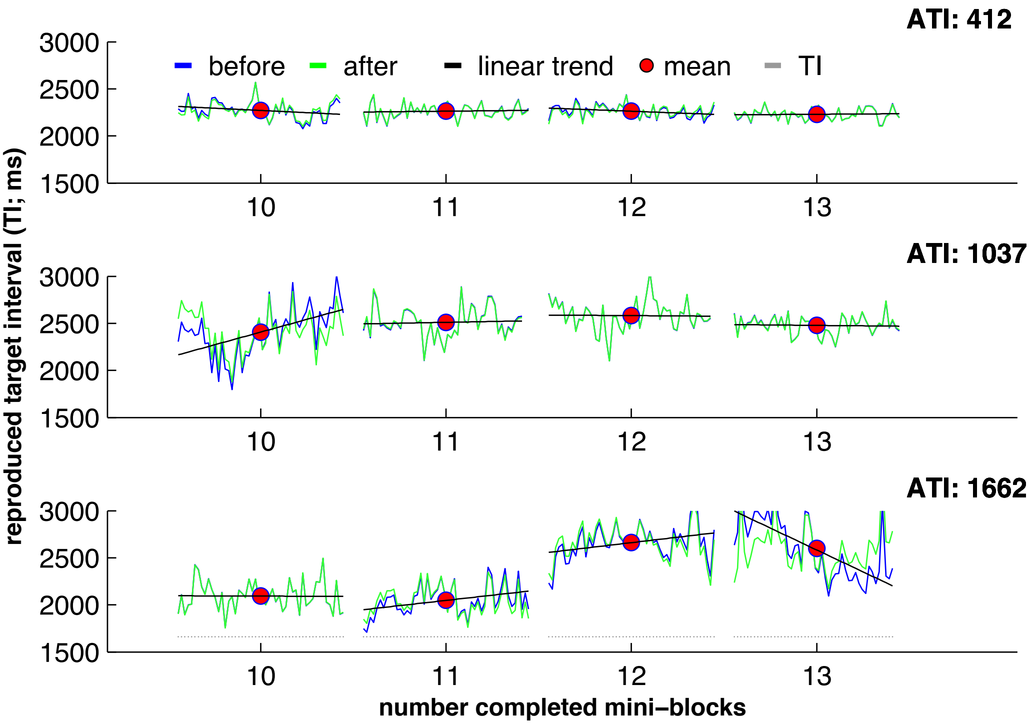


Figure 7.3: Linear de-trending of data (1st step). Gradual acquisition, or attenuation, of bias in time interval reproduction may affect the observed standard deviation instead of originating from participants' "true variability" in performance. To account for this bias, we removed linear trends from the data, separately for each mini-block (i.e. 50 trials uninterrupted by feedback) separately. TI: target interval; ATI: additional target interval.

Second, we removed biases in time reproduction (2nd step), separately for each mini-block. Participants may systematically overestimate the TI on one mini-block while systematically underestimating the TI on another or vice versa (perhaps in an attempt to compensate for bias revealed by feedback, which may then lead to acquisition of bias in the opposite direction on the subsequent block, i.e. overcompensation). We subtracted the difference between a mini-block's mean reproduced TI and the median reproduced TI computed across all mini-blocks from the data, effectively centring the data on the median reproduced TI across mini-blocks. The remaining variability reflects participants' actual variability in time interval reproduction not contaminated by gradual acquisition or attenuation of bias in time reproduction. Analysis of the data without this de-trending procedure showed that our conclusions did not spuriously depend on this procedure.

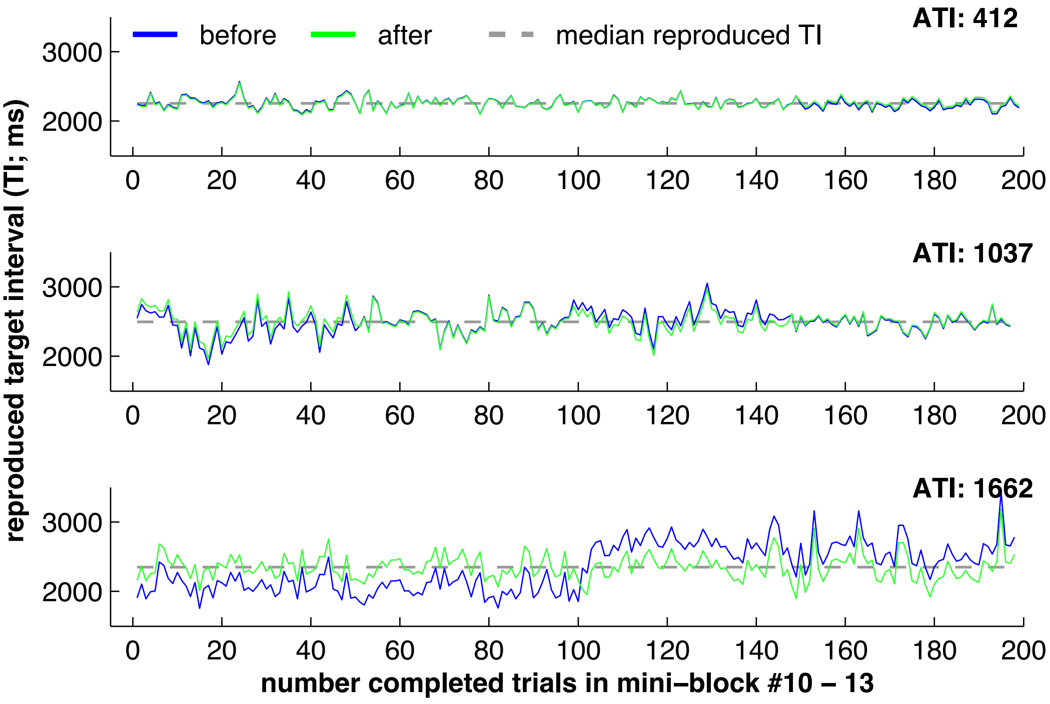


Figure 7.4: Removal of median shifts from the data (2nd step of de-trending procedure). Participants received feedback upon completion of each mini-block (i.e. 50 trials), which was informative about bias in time reproduction. Participants may attempt to compensate for this indicated bias and, in doing so, acquire a bias in the opposite direction (i.e. overcompensation). This results in a shift in the mean of the distribution of reproduced target intervals, but may also affects the observed standard deviation. We therefore removed the difference between the mean of each mini-block and the overall median across mini-blocks from the data.

Analysis of variability and bias in target interval reproduction

We used the data acquired during baseline as predictors in a multiple linear regression analysis to predict observer performance. If participants used both cues, the SET and AS, then both cues should be significant predictors of participants' performance. If participants used one cue only, either the SET or the AS, then only one of the predictors of the linear regression will turn out significant. Bias in time interval reproduction was analysed by computing the mean reproduced TI across all trials. The actual TI (2262ms) was then subtracted from the mean reproduced TI.

Analysis of baseline data

After removal of gradual changes participants' timing performance (de-trending procedure), we first assessed whether participants' performance was different after having completed the experiment compared to the pre-experiment measurement. As we found no change in participants' mean or standard deviation of reproduced TIs, we then pooled the baseline data collected before and after the experiment. To probe for bias in time interval reproduction, the TI (2262ms) and the three ATIs (412ms, 1037ms, 1662ms) were subtracted from the corresponding mean reproduced TIs. We further tested whether bias in time interval reproduction was different during the experiment compared to baseline. We subtracted mean estimated TI during baseline from the mean estimates TI during the experiment. All difference scores were tested against zero using Wilcoxon's signed rank test without correction for multiple comparison, as this would have worked to our advantage in the present case.

Results

Assessment of bias in time estimation

There was no significant difference (all $p > 0.1$) in either the mean or the standard deviation for any of the four time intervals (the three ATIs or the TI) between the pre- and post-experiment baseline measurements (see Figure 7.5). We therefore pooled all analysed pre- and post-experiment baseline trials (= 200 trials) to then compute predictions for Hypothesis 1, 2, and 3 based on a larger number of trials.

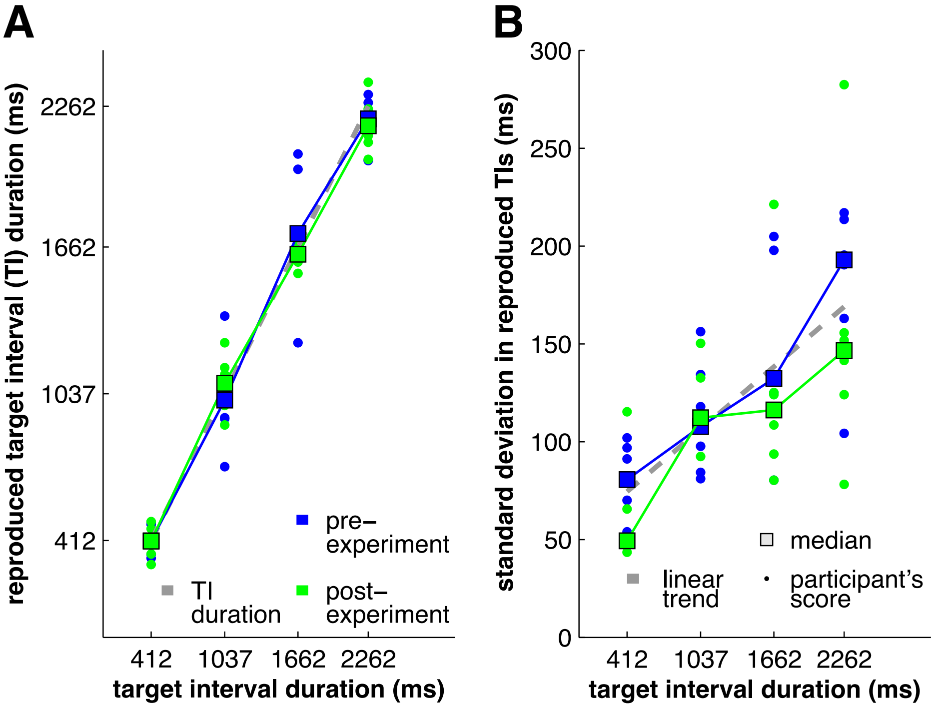


Figure 7.5: No difference in baseline before (pre-) and after (post-) the experiment. A. Participant's mean accuracy in time interval reproduction was comparable before and after the experiment for all four time intervals (p > 0.1). **B.** There was no significant difference in the standard deviation of reproduced target time intervals before and after the experiment (p > 0.1). The linear trend shown here was computed for the pre- and post-experiment baseline measures combined.

While participants exhibited no bias for the three ATIs during baseline (p > 0.1), they underestimated the TI by 3.3% (median difference = -74.7ms, range = -129.2 - 4.2ms; z = -1.992, p = 0.046, r = 0.813). This bias was reduced to 0.5% underestimation during the experiment for the short ATI only (median difference = -15.0ms, range = -44.8 - 42.3ms; z = -1.992, p = 0.046, r = 0.813) while there was no reduction or increase for the intermediate (median difference = -73.6ms, range = -161.7 - 232.2, p > 0.1) and long ATI (median difference = -58.8ms, range = -205.5 - 88.3ms, p > 0.1). *On average*, participants were therefore accurate in their timing.

Importantly, introducing the AS did not induce significant temporal bias. Instead, there was a removal of bias for the most reliable AS (see Figure 7.6).

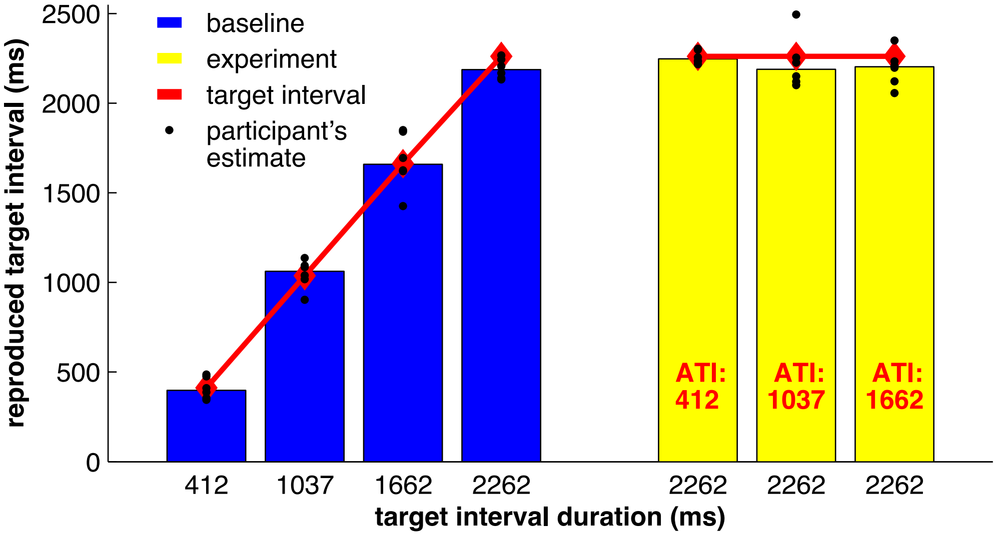


Figure 7.6: Bias in time interval reproduction. Participants accurately reproduced the target interval during baseline except for a 3.3% underestimation of the longest target interval (TI, 2262ms). This underestimation was reduced to 0.5% during the experiment for the shortest additional time interval (ATI: 412ms) while it remained comparable for the intermediate (1037ms) and long ATI (1662ms). Introducing the additional stimulus did not induce a bias in time reproduction.

Sub-optimal improvement in timing accuracy

The multiple linear regression was significant ($R_{adj}^2 = 0.501$, $p < 0.001$) but while the AS was a significant predictor of observed performance ($beta_{AS} = 0.798$, SE = 0.239; t(15) = 3.339, p = 0.005), SET failed to reach significance ($beta_{SET} = 0.251$, SE = 0.206; t(15) = 1.22, p = 0.242). We eliminated SET from the model by backwards elimination (Chatterjee & Hadi, 2006) and computed the reduced model, which again was significant ($R_{adj}^2 = 0.486$, $p < 0.001$). There was no significant drop in variance as a consequence of eliminating SET as a predictor (F(1,15) = 1.486, p > 0.05). These results imply that participants used the SET cue to learn the duration of the ATI but thereafter, participants relied exclusively on the AS to time their responses (see Figure 7.7).

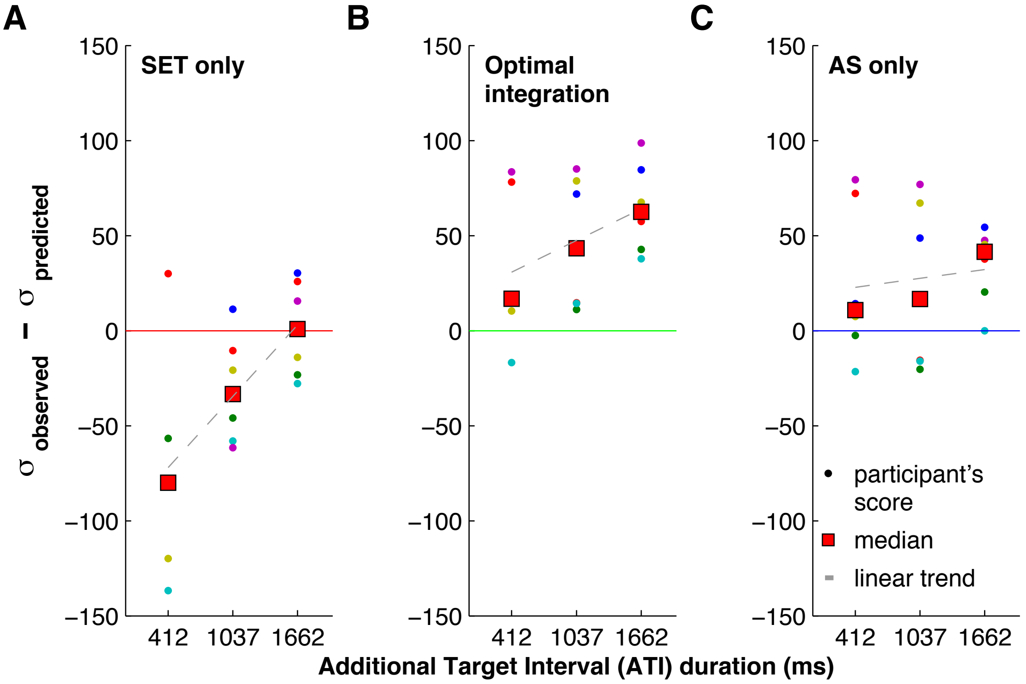


Figure 7.7: Participants do not integrate but rely on the more reliable temporal cue only (AS). Participants' performance during the experiment was evaluated against their individual baseline performance. To illustrate participants' improvement in time interval reproduction during the experiment, we subtracted their predicted performance based on from observed performance during the experiment for each participant and hypothesis separately. **A** Participants performed more accurately than predicted by Hypothesis 1 (SET only) for the short and intermediate ATI. **B** Participants performed less accurately than predicted by Hypothesis 2 (optimal integration) for all three ATIs. **C** Similarly, participants performed less accurately than predicted by Hypothesis 3 for all the ATIs. But the AS turned out to be the only significant predictor in the multiple regression analysis: participants rely on the AS exclusively in timing their motor responses. *Red squares: median difference in standard deviation (predicted – observed performance) across participants for each additional target interval (ATI); coloured circles: single subject data. Dashed grey lines: linear trend across participants' difference scores with ATI duration.*

Increased accumulation of temporal error during ATI estimation

Comparing observed to predicted performance for the winning hypothesis (Hypothesis 3: AS only), the data show an upwards bias in timing accuracy (see Figure 3). In other words, participants were *less* accurate in their timing than predicted by Hypothesis 3 for the short (median difference in SD = 10.8ms, range: -21.5 – 79.4ms), intermediate (median difference in SD = 16.6ms, range: -20.4 –

76.9ms), and long ATI (median difference in SD = 415ms, range: -0.1 – 54.4ms; see Figure 3). Interestingly, this offset was proportional to actual ATI duration (see Figure 4). Such proportional bias may signal that temporal error accumulates more quickly for the ATI during the experiment than during baseline (i.e. a higher Weber fraction; see Figure 7.8). To quantify this bias, we fit the following model to the data:

$$\sigma_R = \alpha\sigma_{ATI} \tag{8}$$

where α is a constant scaling factor that captures the proportional offset observed in the data. In fact, if the standard deviation associated with the three ATIs during the experiment (impossible to assess directly) were 132.1% (i.e. α = 1.321) of the observed standard deviation during baseline, performance predicted by Hypothesis 3 (AS only) closely matched median observed performance (averaged across participants; see Figure 4). R_{adj}^2 dropped to 0.370 (compared to R_{adj}^2 = 0.486 from the linear regression with AS as the only predictor) as a consequence of eliminating the regression constant (cf. $\hat{y} = \beta_1 X_1 + \beta_0$ to Equation 8). Still, the simple model outlined in Equation 8 can account for a significant proportion of the variance in the data ($p < 0.05$). Temporal error may thus accumulate more quickly for the ATIs used during the experiment, when ATIs are marked by the onset of the AS only and not repeated immediately before reproduction, as during baseline. Importantly, no such *constant* increase in temporal error (for the ATI, TI, or both) could bring the observed timing accuracy in alignment with the timing accuracy predicted by both Hypothesis 1 (SET only) and 2 (optimal integration).

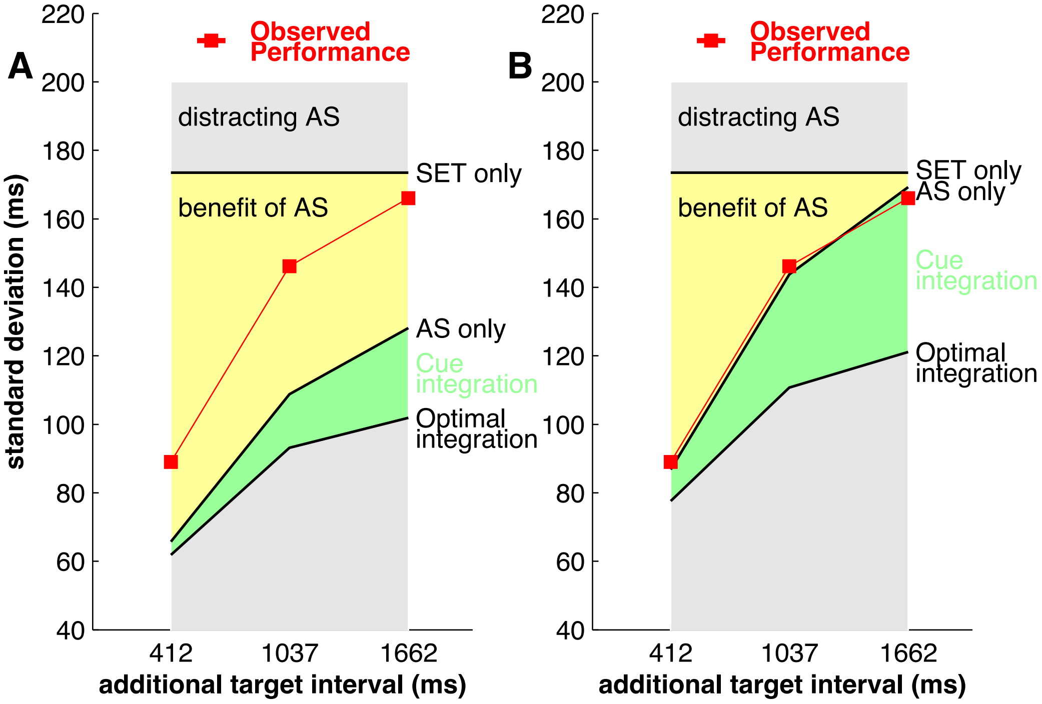


Figure 7.8: Sub-optimal improvement in time reproduction with higher rate of accumulation of temporal error. Participants may ignore the additional stimulus (AS) in which case performance would equal baseline TI performance (black line labelled SET only). Alternatively, performance may improve in the presence of the AS (yellow: benefit of AS; green: cue integration; benefit of AS *and* SET). Performance cannot improve beyond participants' best possible performance during the experiment given their baseline performance (i.e. below *optimal integration*). Observed performance falls in the yellow area, i.e. participants benefit from the AS. **A** Participants use the AS but the observed standard deviation is larger than the predicted standard deviation for Hypothesis 3 (AS only). **B** This offset on observed versus predicted standard deviation is proportional to ATI duration and may as such signal an increased rate in the accumulation of temporal error during the experiment compared to baseline.

Discussion

Whenever performance depends on accurate time perception, it is limited by ITU. We asked whether participants can extract temporal information from multiple cues, all informative about the time for future action, to reduce ITU. Such reduction in ITU would improve performance here by increasing participants' accuracy in time interval reproduction. We found that participants relied exclusively on the AS, the more reliable of the two sensory timing cues, in timing their motor action. But participants have to use the SET to learn the information that the AS carries about the timing of future action. We therefore conclude that while participants can extract temporal information from both sensory cues, they fail to integrate this information. Instead, they use the more reliable timing cue which leads to a sub-optimal improvement in timing accuracy compared to the maximum possible.

In addition, temporal error seems to accumulate more quickly during the experiment compared to baseline. While participants relied on the AS for timing performance, timing accuracy was worse during the experiment compared to baseline. This offset was proportional to the performance during baseline and thus depends on the overall duration of the to-be-estimated time interval. This suggests a higher rate of accumulated temporal error. Distortion of time interval perception induced by changing the context in which the interval is presented has been found before (Droit-Volet & Gil, 2009; Orgs, Bestmann, Schuur, & Haggard, 2011). In the present case, however, the change in context did not lead to a change in clock speed (which would have led to either over- or underestimation, i.e. bias). Instead, there may have been an increase in the rate at which temporal error accumulates (i.e. higher Weber fraction), suggesting that the temporal context in which events occur can change the individual Weber Fraction, very much like context can change clock speed.

A necessary prerequisite for temporal cue combination: multiple timers

Failure of temporal cue combination to improve our sense of the *passage of time* to remove ITU about forthcoming events or actions, is remarkable given previous demonstrations of optimal cue integration in visual (Ernst & Banks, 2002; Ernst & Bülthoff, 2004; Hillis et al., 2004; Knill, 2007; Knill & Saunders, 2003; Oruç et al., 2003), spatial (Fetsch et al., 2010; van Beers, Wolpert, et al., 2002), motor (Bays & Wolpert, 2007; van Beers, Baraduc, et al., 2002; Wolpert, 2007), and even temporal (Elliott et al., 2010; Wing et al., 2010) processing. There are two possible explanations for this failure of temporal cue integration, one relating to the number of "clocks in the brain", and another relating to causal perception.

With regard to the first possible explanation, temporal cue combination critically relies on being able to keep track of more than one time interval at once (TI and ATI). Tracking two time intervals simultaneously is difficult to accommodate with theories and models of time perception that postulate either one centralised timer (Treisman, 1963) or one timer for each sensory modality (Ivry & Schlerf, 2008) when all temporal cues are presented in the same sensory modality (here: vision). Failure of temporal cue combination may therefore be informative about the number of timers in the brain and would limit this number to *one* per sensory modality. Note that such a limit would make it harder for the participants to learn the ATI albeit not impossible (Meck & Church, 1984).

Several studies, however, have shown that human and non-human animals can keep track of multiple time intervals simultaneously when stimuli are presented in either the same (Buhusi & Meck, 2009; Rule, 1986) and different sensory modalities (Leak & Gibbon, 1995; McAuley et al., 2010; Meck & Church, 1984). If, as suggested by these findings, there were indeed multiple timers within one sensory modality, then temporal cue combination should in principle be possible. If participants *can* measure the TI and ATI simultaneously, then all they need to do for optimal cue integration is to combine these two estimates. The observed failure to optimally combine temporal cues thus points towards a more fundamental limitation of temporal cue combination, which we discuss in the following.

Temporal proximity, causal inference, and cue combination

Alternatively, participants failed to integrate the temporal information provided by SET and AS because optimal integration may require that these two visual cues are perceived as manifestations of one single underlying (but hidden) object (Welch

& Warren, 1980). In depth perception, for example, visual and haptic information are both caused by the size and shape of one single object (Ernst & Banks, 2002). Similarly, visual and proprioceptive information are both caused by the position of one's hand in space (van Beers, Wolpert, et al., 2002). Indeed, we know that explicit knowledge about a common cause promotes cue integration (Helbig & Ernst, 2007). In the present case, there was no *obvious* single object that could have caused the two visual percepts (i.e. SET and AS), suggesting that the failure of temporal cue integration resulted from the underlying failure to bind these two visual percepts to one single underlying but hidden object. If the case, cue combination is no general-purpose mechanism for sensory-motor noise reduction but instead features in causal inference and object recognition. Conversely, cue combination itself may enable the perception of a common underlying object of sensory percepts. In other words, rather than regarding cue combination as the consequence of binding percepts to a common cause, the perception of a common cause may only be possible through successful cue combination. Percepts that are unlikely to have a common cause then limit cue combination, but in doing so prevent faulty inference (e.g. inferring the existence of a common cause of sensory percepts when there is none).

Spatial (Meredith & Stein, 1996) and temporal proximity (Paul Bertelson & Aschersleben, 2003; Colonius & Diederich, 2010; Meredith, Nemitz, & Stein, 1987) are reliable cues for correctly inferring the existence of a common underlying object of separate sensory percepts (Körding et al., 2007). Recent work shows that temporal *correlation* also determines whether or not cue combination occurs (Parise, Spence, & Ernst, 2012). It may thus serve as yet another cue to infer the common cause of sensory percepts. In the present experiment, the SET and AS were perfectly correlated, but not temporally proximate (i.e. outside the "typical" window of integration; Bertelson & Aschersleben, 2003; Hartcher-O'Brien & Alais, 2011). Temporal proximity may therefore be a necessary requirement for cue combination to happen. But if temporal proximity is indeed a necessary requirement for cue combination and perception of a common cause, then participants will never integrate *multiple* cues that signal common action or event timing but are distributed over time. Our sense of the *passage of time* cannot be improved by multiple cues. Instead, we rely on the most reliable and informative cue. This does imply, however, that cue integration is best understood as a mechanism that features in causal inference and object recognition rather than a general-purpose mechanism for sensory-motor noise reduction.

Temporally distal sensory percepts, however, *can* originate from a single object. Just think about watching a lighthouse at night from afar: the sensory cue for its existence is the periodically re-occurring ray of light separated by a temporal interval. But *even if* two sensory percepts originate from two separate objects, they can still be informative about the same property (here: action timing). Integration of such percepts would lead to an improved estimate of this specific property. But if temporal proximity (or the inference to a common cause) is indeed a necessary requirement for *cue combination*, then information provided by separate objects about common properties is ignored to the detriment of performance. The cost of a faulty inference (e.g. inferring a common object when there is none) may outweigh the benefits of having more precise sensory estimates of external properties. And if sensory percepts are temporally distal, then a common cause may be unlikely (Weisswange, Rothkopf, Rodemann, & Triesch, 2011). This does imply, however, that cue combination is understood as a feature in causal inference and object recognition. If cue combination were a general-purpose mechanism for sensory-motor noise reduction, then consideration about the cost of faulty inference should not matter.

Finally, our limited capacity to integrate information provided by multiple cues distributed over time may also be dictated by the “architecture” of our brains.

Integration requires the interaction of neural activity that encodes the information of separate to-be-integrated cues (the neural activity has to “meet in the brain”; Meredith et al., 1987). The interactions between these neural representations then determine behaviour (e.g. cue integration). We know that timing cues can trigger *sustained* neural activity that relates to the to-be-timed intervals (Janssen & Shadlen, 2005; Leon & Shadlen, 2003; Mita et al., 2009) (e.g. a gradual build-up in neural activity associated with the duration of to-be-timed intervals; Mita, Mushiake, Shima, Matsuzaka, & Tanji, 2009). The integration of temporally segregated cues then requires a superordinate “integrator” that integrates information encoded by multiple timers (i.e. their respective neural activity). Combined input into this integrator from the various timers should improve time estimation (i.e. the integrator’s output), compared to inputs from a single internal clock, which is the fundamental principle of cue integration: two noisy sensory signals lead to a better sensory estimate than one sensory signal only; Ernst & Banks, 2002; Oruç et al., 2003).

Previous work has demonstrated such integrators for converging sensory inputs in the spatial domain (Meredith & Stein, 1983), and behavioural studies on bi- or tri-manual tapping suggest a mechanism that ensures the synchronisation of motor actions (Helmuth & Ivry, 1996; Ivry & Richardson, 2002), which effectively acts as an integrator. Assuming that multiple time intervals can be tracked simultaneously (Meck & Church, 1984; Rule, 1986; i.e. that there are multiple internal clocks that can encode different time intervals at the same time), the failure to reduce the rate of accumulation of temporal error through temporal cue combination shown here suggests lack of an integrator for time.

Conclusion

We here report a striking failure of optimal cue integration in the temporal domain. Being provided with two sensory cues that both inform about the correct timing of a forthcoming action, participants fail to integrate these cues but instead rely on the more reliable cue only. This suggests that cue integration occurs only when sensory percepts are perceived as the manifestations of one single object or common cause. Temporal proximity of sensory percepts may be an essential prerequisite for inference of a common cause and sensory cue integration, and limits the use of multiple cues distributed across time to improve our sense of the passage of time.

Chapter 8: General Conclusions

Abstract: A summary of the main findings presented in Chapter 2 – 7 clearly shows the fundamental difference between external (ETU) and internal temporal uncertainty (ITU) – two types of temporal uncertainty distinguished by *origin*. ETU and ITU differ in their effects on temporal preparation, their interaction with event preparation, and reward-based decision-making. Manipulation of ETU, as opposed to ITU, which had been manipulated previously, allowed us to distinguish between competing explanations for changes in cortico-spinal excitability (CSE) prior to imperative events measured by Transcranial Magnetic Stimulation (TMS). Having revealed the influence of ITU on behaviour, we explored whether participants could reduce ITU by extraction and combination of temporal information from multiple cues. While participants failed to combine information provided by multiple cues, they selected the temporally more reliable cue for action timing, which shows that they are clearly sensitive to differences in ITU. Taken together, this thesis presents an in depth exploration of behaviour under temporal uncertainty and reveals that the *origin* of uncertainty matters for its effects on behaviour.

Keywords: action preparation, temporal preparation, event preparation, reward-based decision making, temporal uncertainty, ETU, ITU, event uncertainty, cue combination

Temporal uncertainty affects preparation for imperative events (Chapter 2-5), accurate action timing in case such events are lacking (Chapter 6-7), and decisions between alternative actions if their outcome depends on accurate timing (Chapter 7). We here distinguished between two types of temporal uncertainty: *external* (ETU) and *internal* temporal uncertainty (ITU). External temporal uncertainty originates in the environment and arises if imperative events, or the appropriate time for action if such events are lacking, vary from one instance to the next. Internal temporal uncertainty is due to an organism's limited accuracy in keeping track of the passage of time, which increases in direct proportion to the duration of time intervals to-be-judged (Gibbon, 1977; Gibbon & Allan, 1984; Lewis & Miall, 2009; Rakitin et al., 1998).

We here demonstrated, for the first time, that the *origin* of temporal uncertainty, besides its level, determines how temporal uncertainty influences temporal preparation (Chapter 2), event preparation (Chapter 3), and decision-making (Chapter 6). ETU and ITU interact in their effects on temporal preparation (Chapter 1). High levels of ITU may mask effects of ETU (Chapter 1). Effects of ETU and ITU on temporal preparation are under executive control and can be fully removed by accurate, explicit information about the timing of imperative events (Chapter 1). The effects of ETU and ITU, however, may not be fully dissociable – we only observed a complete removal of effects of ETU and ITU on temporal preparation once accurate and explicit information about the timing of imperative events removed the need to keep track of the passage of time entirely (as opposed to selectively removing ITU: cf. Experiment 1 & 2 in Chapter 1). This finding may explain why others have reported residual effects of temporal uncertainty despite removal of ETU by accurate and explicit information (Los & van den Heuvel, 2001; Los & Heslenfeld, 2005). If participants are not provided with continuous temporal information throughout the preparatory interval, they still experience ITU, which may lead to residual effects of temporal uncertainty (Los & van den Heuvel, 2001; Los & Heslenfeld, 2005). We conclude that effects of ETU and ITU are under executive control and not due to automatic conditioning processes, as previously suggested by Los and colleagues (Los, Knol, & Boers, 2001; but see Los & Horoufchin, 2011). While ETU and ITU have differential effects on temporal preparation, they are not fully dissociable and can only be removed fully in conjunction by taking away the necessity to keep track of time entirely.

We further demonstrated that both ETU and ITU interact with event preparation. Crucially, the type of interaction differed for ETU versus ITU, thus revealing yet another important influence of the *origin* of temporal uncertainty on human cognitive motor control. When participants know *what* action to prepare for (i.e. low event uncertainty), then they maximally benefit from low ETU. When event uncertainty is high, then they fail to benefit from low ETU. By contrast, participants can compensate for high ITU but only when they know *what* action to prepare for. This interaction between temporal and event preparation had been overlooked so far, despite extensive research (Bertelson & Barzeele, 1965; Bertelson & Boons, 1960;

Sanders, 1990; Spijkers, 1990; Spijkers & Walter, 1985), due to lack of a distinction between ETU and ITU.

Finally, in deciding between alternative actions, whose outcomes depend on accurate action timing, participants distort ETU but not ITU (Chapter 6). This shows the important distinction between ETU and ITU in yet another area in human information processing: decision-making. In addition, our findings build an important bridge between classic studies on decision making, with their focus on external risk and uncertainty (Allais, 1953; Daniel Kahneman & Tversky, 1979, 2000; Tversky & Kahneman, 1992), and more recent studies on how participants cope with uncertainties inherent in motor performance (Hudson, Maloney, & Landy, 2007; Hudson et al., 2008; Trommershäuser, 2009; Trommershäuser et al., 2006, 2003). The difference in *origin* explains why participants distort probabilities under conditions of external but not internal uncertainty.

In two studies, using Transcranial Magnetic Stimulation (TMS) to probe cortico-spinal excitability (CSE; Chapter 4) and intracortical inhibitory circuits (Chapter 5), we further explored the nature of temporal and event preparation. More specifically, we aimed to distinguish between different proposals – in particular *response competition*, *impulse control*, and *noise reduction* – all aimed at explaining changes in CSE prior to imperative events. Whereas others have manipulated ITU to study the development of CSE prior to imperative events (Hasbroucq, Osman, et al., 1999; Hasbroucq et al., 1997), we manipulated ETU (Chapter 4). We found that *response competition* in combination with *impulse control* can best explain changes in CSE prior to imperative events. Our attempts to further explore this modulation of CSE by selectively probing intracortical inhibitory circuits did not lead to conclusive results (Chapter 5). We speculate that short intracortical inhibition supports *impulse control* while long intracortical inhibition implements *response competition*. Further studies will have to verify our speculations.

Finally, having revealed the importance of distinguishing between ETU and ITU, and the potentially detrimental effects of high levels of ITU on temporal and event preparation, we turned towards exploring strategies to reduce ITU. In case participants lack precise, external time-keepers (such as stop-watches, cf. Experiment 3 in Chapter 1), they might potentially combine temporal information from multiple cues to reduce ITU. The beneficial effects of cue combination on sensory estimates have been shown in many other domains of human information processing (Ernst & Banks, 2002; Ernst & Bülthoff, 2004; Fetsch et al., 2009; Hillis et al., 2004; Oruç et al., 2003). In stark contrast to this literature, participants failed to combine temporal information from multiple cues. Instead, they selected the most reliable cue to time their actions. Participants are thus sensitive to differences in ITU but fail to combine temporal information from multiple cues.

Taken together, this thesis presents an in depth exploration of the differential effects of two types of temporal uncertainty: ETU and ITU, which are distinguished by origin. Results show that the *origin* determines how temporal uncertainty affects human cognitive motor control and reward-based decision making. As such, this thesis makes an important contribution to the growing field of study of behaviour under uncertainty. Where uncertainty comes from matters for human cognitive motor control and reward-based decision making. As we typically experience uncertainty about almost every aspect in life (except, of course, analytical truths: 1 + 1 = 2), the study of behaviour under uncertainty is directly relevant to every day decisions and actions.

References

Alegria, J. (1974). The time course of preparation after a first peak: Some constraints of reacting mechanisms. *The Quarterly Journal of Experimental Psychology*, *26*(4), 622–632.

Alegria, J., & Delhaye-Rembaux, M. (1975). Sequential effects of foreperiod duration and conditional probability of the signal in a choice reaction time task. *Acta Psychologica*, *39*(5), 321–328.

Allais, M. (1953). Le Comportement de l'Homme Rationnel devant le Risque: Critique des Postulats et Axiomes de l'Ecole Americaine. *Econometrica*, *21*(4), 503–546.

Allman, M. J., & Meck, W. H. (2012). Pathophysiological distortions in time perception and timed performance. *Brain, 135*, 656-677.

Arieh, Y., & Marks, L. E. (2008). Cross-modal interaction between vision and hearing: a speed-accuracy analysis. *Perception & Psychophysics*, *70*(3), 412–421.

Artieda, J., Pastor, M. A., Lacruz, F., & Obeso, J. A. (1992). Temporal discrimination is abnormal in Parkinson's disease. *Brain*, *115(1*), 199–210.

Avoli, M., Hwa, G., Louvel, J., Kurcewicz, I., Pumain, R., & Lacaille, J. C. (1997). Functional and pharmacological properties of GABA-mediated inhibition in the human neocortex. *Canadian Journal of Physiology and Pharmacology*, *75*(5), 526–534.

Baier, B., Kleinschmidt, A., & Müller, N. G. (2006). Cross-modal processing in early visual and auditory cortices depends on expected statistical relationship of multisensory information. *The Journal of Neuroscience*, *26*(47), 12260–12265.

Balci, F., Freestone, D., & Gallistel, C. R. (2009). Risk assessment in man and mouse. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(7), 2459–2463.

Bays, P. M., & Wolpert, D. M. (2007). Computational principles of sensorimotor control that minimize uncertainty and variability. *The Journal of Physiology*, *578*(2), 387–396.

Bertelson, P. (1967). The time course of preparation. *The Quarterly Journal of Experimental Psychology*, *19*(3), 272–279.

Bertelson, P., & Barzeele, J. (1965). Interaction of time-uncertainty and relative signal frequency in determining choice reaction time. *Journal of Experimental Psychology*, *70*(5), 448–451.

Bertelson, P., & Boons, J.-P. (1960). Time Uncertainty and Choice Reaction Time. *Nature*, *187*(4736), 531–532.

Bertelson, P., & Tisseyre, F. (1968). The time-course of preparation with regular and irregular foreperiods. *The Quarterly Journal of Experimental Psychology*, *20*(3), 297–300.

Bertelson, P., & Aschersleben, G. (2003). Temporal ventriloquism: crossmodal interaction on the time dimension. 1. Evidence from auditory-visual temporal order judgment. *International Journal of Psychophysiology, 50*(1-2), 147–155.

Bertelson, P., & Barzeele, J. (1965). Interaction of time-uncertainty and relative signal frequency in determining choice reaction time. *Journal of Experimental Psychology*, *70*(5), 448–451.

Bestmann, S., Harrison, L. M., Blankenburg, F., Mars, R. B., Haggard, P., Friston, K. J., & Rothwell, J. C. (2008). Influence of uncertainty and surprise on human corticospinal excitability during preparation for action. *Current Biology*, *18*(10), 775–780.

Borst, U., & Cohen, R. (1987). Impact of time estimation on the crossover effect in schizophrenia. *Psychiatry Research*, *22*(4), 331–340.

Borst, U., & Cohen, R. (1989). Filling the preparatory interval with temporal information or visual noise: crossover effect in schizophrenics and controls. *Psychological Medicine*, *19*(4), 865–874.

Boulinguez, P., Jaffard, M., Granjon, L., & Benraiss, A. (2008). Warning signals induce automatic EMG activations and proactive volitional inhibition: evidence from analysis of error distribution in simple RT. *Journal of Neurophysiology*, *99*(3), 1572–1578.

Brasil-Neto, J. P., Cohen, L. G., Panizza, M., Nilsson, J., Roth, B. J., & Hallett, M. (1992). Optimal focal transcranial magnetic activation of the human motor cortex: effects of coil orientation, shape of the induced current pulse, and stimulus intensity. *Journal of Clinical Neurophysiology*, *9*(1), 132–136.

Bueti, D., Bahrami, B., Walsh, V., & Rees, G. (2010). Encoding of temporal probabilities in the human brain. *The Journal of Neuroscience*, *30*(12), 4343–4352.

Buhusi, C. V., & Meck, W. H. (2005). What makes us tick? Functional and neural mechanisms of interval timing. *Nature Reviews. Neuroscience*, *6*(10), 755–765.

Buhusi, C. V., & Meck, W. H. (2009). Relativity Theory and Time Perception: Single or Multiple Clocks? *PLoS ONE*, *4*(7), e6268.

Burle, B., Bonnet, M., Vidal, F., Possamaï, C.-A., & Hasbroucq, T. (2002). A transcranial magnetic stimulation study of information processing in the motor cortex: relationship between the silent period and the reaction time delay. *Psychophysiology*, *39*(2), 207–217.

Burr, D., Banks, M. S., & Morrone, M. C. (2009). Auditory dominance over vision in the perception of interval duration. *Experimental Brain Research, 198*(1), 49–57.

Carlsen, A. N., & Mackinnon, C. D. (2010). Motor preparation is modulated by the resolution of the response timing information. *Brain Research*, *1322*, 38–49.

Carroll, C. A., Boggs, J., O'Donnell, B. F., Shekhar, A., & Hetrick, W. P. (2008). Temporal processing dysfunction in schizophrenia. *Brain and Cognition*, *67*(2), 150–161.

Carroll, C. A., O'Donnell, B. F., Shekhar, A., & Hetrick, W. P. (2009). Timing dysfunctions in schizophrenia span from millisecond to several-second durations. *Brain and Cognition*, *70*(2), 181–190.

Cash, R. F. H., Ziemann, U., Murray, K., & Thickbroom, G. W. (2010). Late cortical disinhibition in human motor cortex: a triple-pulse transcranial magnetic stimulation study. *Journal of Neurophysiology*, *103*(1), 511–518.

Chatterjee, S., & Hadi, A. S. (2006). *Regression Analysis by Example* (4th ed.). Wiley-Interscience.

Chen, R., Seo, D.-O., Bell, E., von Gall, C., & Lee, C. (2008). Strong resetting of the mammalian clock by constant light followed by constant darkness. *The Journal of Neuroscience*, *28*(46), 11839–11847.

Chen, R. (2004). Interactions between inhibitory and excitatory circuits in the human motor cortex. *Experimental Brain Research*, *154*(1), 1–10.

Chu, J., Gunraj, C., & Chen, R. (2008). Possible differences between the time courses of presynaptic and postsynaptic GABAB mediated inhibition in the human motor cortex. *Experimental Brain Research*, *184*(4), 571–577.

Cisek, P. (2006). Integrated neural processes for defining potential actions and deciding between them: a computational model. *The Journal of Neuroscience*, *26*(38), 9761–9770.

Cisek, P. (2007). Cortical mechanisms of action selection: the affordance competition hypothesis. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *362*(1485), 1585–1599.

Cisek, P., & Kalaska, J. F. (2005). Neural correlates of reaching decisions in dorsal premotor cortex: specification of multiple direction choices and final selection of action. *Neuron*, *45*(5), 801–814.

Cisek, P., & Kalaska, J. F. (2010). Neural Mechanisms for Interacting with a World Full of Action Choices. *Annual Review of Neuroscience, 33*, 269-298.

Colonius, H., & Diederich, A. (2010). The optimal time window of visual-auditory integration: a reaction time analysis. *Frontiers in Integrative Neuroscience*, *4*: 11.

Connors, B. W., Malenka, R. C., & Silva, L. R. (1988). Two inhibitory postsynaptic potentials, and GABAA and GABAB receptor-mediated responses in neocortex of rat and cat. *The Journal of Physiology*, *406*, 443–468.

Correa, A., & Nobre, A. C. (2008). Neural modulation by regularity and passage of time. *Journal of Neurophysiology*, *100*(3), 1649–1655.

Cotti, J., Rohenkohl, G., Stokes, M., Nobre, A. C., & Coull, J. T. (2011). Functionally dissociating temporal and motor components of response preparation in left intraparietal sulcus. *NeuroImage*, *54*(2), 1221–1230.

Coull, J. T., Frith, C. D., Büchel, C., & Nobre, A. C. (2000). Orienting attention in time: behavioural and neuroanatomical distinction between exogenous and endogenous shifts. *Neuropsychologia*, *38*(6), 808–819.

Coull, J., & Nobre, A. (2008). Dissociating explicit timing from temporal expectation with fMRI. *Current Opinion in Neurobiology*, *18*(2), 137–144.

Coull, J. T., Cheng, R.-K., & Meck, W. H. (2011). Neuroanatomical and neurochemical substrates of timing. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *36*(1), 3–25.

Coxon, J. P., Stinear, C. M., & Byblow, W. D. (2006). Intracortical inhibition during volitional inhibition of prepared action. *Journal of Neurophysiology*, *95*(6), 3371–3383.

Cui, X., Stetson, C., Montague, P. R., & Eagleman, D. M. (2009). Ready...go: Amplitude of the FMRI signal encodes expectation of cue arrival time. *PLoS Biology*, *7*(8), e1000167.

Davey, K. (2008). Magnetic field stimulation: the brain as a conductor. *The Oxford Handbook of Transcranial Magnetic Stimulation* (pp. 33–46). New York, USA: Oxford University Press.

Davis, R. (1962). Time Uncertainty and the Estimation of Time-intervals. *Nature*, *195*(4838), 311–312.

Davranche, K., Tandonnet, C., Burle, B., Meynier, C., Vidal, F., & Hasbroucq, T. (2007). The dual nature of time preparation: neural activation and suppression revealed by transcranial magnetic stimulation of the motor cortex. *The European Journal of Neuroscience*, *25*(12), 3766–3774.

Daw, N. D., Niv, Y., & Dayan, P. (2005). Uncertainty-based competition between prefrontal and dorsolateral striatal systems for behavioral control. *Nature Neuroscience*, *8*(12), 1704–1711.

Dayan, P., & Daw, N. D. (2008). Decision theory, reinforcement learning, and the brain. *Cognitive, Affective & Behavioral Neuroscience*, *8*(4), 429–453.

De Martino, B., Kumaran, D., Seymour, B., & Dolan, R. J. (2006). Frames, biases, and rational decision-making in the human brain. *Science*, *313*(5787), 684–687.

Deisz, R. A. (1999a). GABA(B) receptor-mediated effects in human and rat neocortical neurones in vitro. *Neuropharmacology*, *38*(11), 1755–1766.

Deisz, R. A. (1999b). The GABA(B) receptor antagonist CGP 55845A reduces presynaptic GABA(B) actions in neocortical neurons of the rat in vitro. *Neuroscience*, *93*(4), 1241–1249.

Di Lazzaro, V., Oliviero, A., Saturno, E., Dileone, M., Pilato, F., Nardone, R., Ranieri, F., et al. (2005). Effects of lorazepam on short latency afferent inhibition and short latency intracortical inhibition in humans. *The Journal of Physiology*, *564*(2), 661–668.

Di Lazzaro, V., Pilato, F., Dileone, M., Profice, P., Ranieri, F., Ricci, V., Bria, P., et al. (2007). Segregating two inhibitory circuits in human motor cortex at the level of GABAA receptor subtypes: a TMS study. *Clinical Neurophysiology,* *118*(10), 2207–2214.

Di Lazzaro, V., Pilato, F., Dileone, M., Ranieri, F., Ricci, V., Profice, P., Bria, P., et al. (2006). GABAA receptor subtype specific enhancement of inhibition in human motor cortex. *The Journal of Physiology*, *575*(3), 721–726.

Drazin, D. H. (1961). Effects of foreperiod, foreperiod variability, and probability of stimulus occurrence on simple reaction time. *Journal of Experimental Psychology*, *62*(1), 43–50.

Droit-Volet, S., & Gil, S. (2009). The time–emotion paradox. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *364*(1525), 1943–1953.

Duclos, Y., Schmied, A., Burle, B., Burnet, H., & Rossi-Durand, C. (2008). Anticipatory changes in human motoneuron discharge patterns during motor preparation. *The Journal of Physiology*, *586*(4), 1017–1028.

Duque, J., Mazzocchio, R., Dambrosia, J., Murase, N., Olivier, E., & Cohen, L. G. (2005). Kinematically specific interhemispheric inhibition operating in the process of generation of a voluntary movement. *Cerebral Cortex*, *15*(5), 588–593.

Duque, J., & Ivry, R. B. (2009). Role of corticospinal suppression during motor preparation. *Cerebral Cortex*, *19*(9), 2013–2024.

Duque, J., Lew, D., Mazzocchio, R., Olivier, E., & Ivry, R. B. (2010). Evidence for two concurrent inhibitory mechanisms during response preparation. *The Journal of Neuroscience, 30*(10), 3793–3802.

Elliott, M. T., Wing, A. M., & Welchman, A. E. (2010). Multisensory cues improve sensorimotor synchronisation. *The European Journal of Neuroscience*, *31*(10), 1828–1835.

Epstein, C. (2008). Electromagnetism. *The Oxford Handbook of Transcranial Magnetic Stimulation* (pp. 3–7). New York, USA: Oxford University Press.

Ernst, M. O. (2007). Learning to integrate arbitrary signals from vision and touch. *Journal of Vision*, *7*(5), 7.1–14.

Ernst, M. O., & Banks, M. S. (2002). Humans integrate visual and haptic information in a statistically optimal fashion. *Nature*, *415*(6870), 429–433.

Ernst, M. O., & Bülthoff, H. H. (2004). Merging the senses into a robust percept. *Trends in Cognitive Sciences*, *8*(4), 162–169.

Fetsch, C. R., DeAngelis, G. C., & Angelaki, D. E. (2010). Visual-vestibular cue integration for heading perception: applications of optimal cue integration theory. *European Journal of Neuroscience*, *31*(10), 1721–1729.

Fetsch, C. R., Turner, A. H., DeAngelis, G. C., & Angelaki, D. E. (2009). Dynamic reweighting of visual and vestibular cues during self-motion perception. *The Journal of Neuroscience*, *29*(49), 15601–15612.

Fitts, P. M. (1992). The information capacity of the human motor system in controlling the amplitude of movement. 1954. *Journal of Experimental Psychology. General*, *121*(3), 262–269.

FITTS, P. M. (1954). The information capacity of the human motor system in controlling the amplitude of movement. *Journal of Experimental Psychology*, *47*(6), 381–391.

Fitts, P. M., & Peterson, J. R. (1964). Information capacity of discrete motor responses. *Journal of Experimental Psychology*, *67*, 103–112.

Fitzgerald, P. B., Maller, J. J., Hoy, K., Farzan, F., & Daskalakis, Z. J. (2009). GABA and cortical inhibition in motor and non-motor regions using combined TMS-EEG: a time analysis. *Clinical Neurophysiology, 120*(9), 1706–1710.

Flanders, M. (2011). What is the biological basis of sensorimotor integration? *Biological Cybernetics*, *104*(1-2), 1–8.

Floeter, M. K., & Rothwell, J. C. (1999). Releasing the brakes before pressing the gas pedal. *Neurology*, *53*(4), 664–665.

Florian, J., Müller-Dahlhaus, M., Liu, Y., & Ziemann, U. (2008). Inhibitory circuits and the nature of their interactions in the human motor cortex – a pharmacological TMS study. *The Journal of Physiology*, *586*(2), 495–514.

Friedman, M., & Savage, L. (1948). The utility analysis of choices involving risk. *Journal of Political Economy*, *56*(4), 279–304.

Garry, M. I., & Thomson, R. H. S. (2009). The effect of test TMS intensity on short-interval intracortical inhibition in different excitability states. *Experimental Brain Research*, *193*(2), 267–274.

Gepshtein, S., Seydell, A., & Trommershäuser, J. (2007). Optimality of human movement under natural variations of visual-motor uncertainty. *Journal of Vision*, *7*(5), 13.1–18.

Gibbon, J. (1977). Scalar expectancy theory and Weber's law in animal timing. *Psychological Review*, *84*, 279–325.

Gibbon, John, & Allan, L. (1984). *Timing and time perception*. New York Academy of Sciences.

Girshick, A. R., & Banks, M. S. (2009). Probabilistic combination of slant information: weighted averaging and robustness as optimal percepts. *Journal of Vision*, *9*(9), 8.1–20.

Gottsdanker, R. (1975). The attaining and maintaining of preparation. *Attention and performance V.* (pp. 33–42). London: Academic Press.

Grondin, S., & Rousseau, R. (1991). Judging the relative duration of multimodal short empty time intervals. *Perception & Psychophysics*, *49*(3), 245–256.

Grondin, S., & Killeen, P. R. (2009). Tracking time with song and count: different Weber functions for musicians and nonmusicians. *Attention, Perception & Psychophysics*, *71*(7), 1649–1654.

Grube, M., Lee, K.-H., Griffiths, T. D., Barker, A. T., & Woodruff, P. W. (2010). Transcranial magnetic theta-burst stimulation of the human cerebellum distinguishes absolute, duration-based from relative, beat-based perception of subsecond time intervals. *Frontiers in Psychology*, *1*: 171.

Gutyrchik, E., Churan, J., Meindl, T., Bokde, A. L. W., von Bernewitz, H., Born, C., Reiser, M., et al. (2010). Functional neuroimaging of duration discrimination on two different time scales. *Neuroscience Letters*, *469*(3), 411–415.

Hackley, S. A. (2009). The speeding of voluntary reaction by a warning signal. *Psychophysiology*, *46*(2), 225–233.

Hackley, S. A., Langner, R., Rolke, B., Erb, M., Grodd, W., & Ulrich, R. (2009). Separation of phasic arousal and expectancy effects in a speeded reaction time task via fMRI. *Psychophysiology*, *46*(1), 163–171.

Harrington, D. L., Castillo, G. N., Fong, C. H., & Reed, J. D. (2011). Neural underpinnings of distortions in the experience of time across senses. *Frontiers in Integrative Neuroscience*, *5*: 32.

Hartcher-O'Brien, J., & Alais, D. (2011). Temporal ventriloquism in a purely temporal context. *Journal of Experimental Psychology. Human Perception and Performance*, *37*(5), 1383–1395.

Hasbroucq, T., Akamatsu, M., Burle, B., Bonnet, M., & Possamaï, C. A. (2000). Changes in spinal excitability during choice reaction time: the H reflex as a probe of information transmission. *Psychophysiology*, *37*(3), 385–393.

Hasbroucq, T., Kaneko, H., Akamatsu, M., & Possamaï, C. A. (1997). Preparatory inhibition of cortico-spinal excitability: a transcranial magnetic stimulation study in man. *Brain Research. Cognitive Brain Research*, *5*(3), 185–192.

Hasbroucq, T., Kaneko, H., Akamatsu, M., & Possamaï, C. A. (1999). The time-course of preparatory spinal and cortico-spinal inhibition: an H-reflex and transcranial magnetic stimulation study in man. *Experimental Brain Research*, *124*(1), 33–41.

Hasbroucq, T., Osman, A., Possamaï, C. A., Burle, B., Carron, S., Dépy, D., Latour, S., et al. (1999). Cortico-spinal inhibition reflects time but not event preparation: neural mechanisms of preparation dissociated by transcranial magnetic stimulation. *Acta Psychologica*, *101*(2-3), 243–266.

Hashimoto, T., Inaba, D., Matsumura, M., & Naito, E. (2004). Two different effects of transcranial magnetic stimulation to the human motor cortex during the pre-movement period. *Neuroscience Research*, *50*(4), 427–436.

Hau, R., Pleskac, T. J., Kiefer, J., & Hertwig, R. (2008). The description–experience gap in risky choice: the role of sample size and experienced probabilities. *Journal of Behavioral Decision Making*, *21*(5), 493–518.

Heinrich, M., Warmbold, A., Hoffmann, S., Firzlaff, U., & Wiegrebe, L. (2011). The sonar aperture and its neural representation in bats. *The Journal of Neuroscience*, *31*(43), 15618–15627.

Helbig, H. B., & Ernst, M. O. (2007). Knowledge about a common source can promote visual- haptic integration. *Perception*, *36*(10), 1523–1533.

Helmuth, L. L., & Ivry, R. B. (1996). When two hands are better than one: reduced timing variability during bimanual movements. *Journal of Experimental Psychology. Human Perception and Performance*, *22*(2), 278–293.

Hertwig, R., & Erev, I. (2009). The description-experience gap in risky choice. *Trends in Cognitive Sciences*, *13*(12), 517–523.

Hick, W. E. (1952). On the rate gain of information. *Quarterly Journal of Experimental Psychology*, *4*, 11–26.

Hilbig, B. E., & Glöckner, A. (2011). Yes, they can! Appropriate weighting of small probabilities as a function of information acquisition. *Acta Psychologica*, *138*(3), 390–396.

Hillis, J. M., Ernst, M. O., Banks, M. S., & Landy, M. S. (2002). Combining sensory information: mandatory fusion within, but not between, senses. *Science*, *298*(5598), 1627–1630.

Hillis, J. M., Watt, S. J., Landy, M. S., & Banks, M. S. (2004). Slant from texture and disparity cues: optimal cue combination. *Journal of Vision*, *4*(12), 967–992.

Hohle, R. H. (1965). Inferred components of reaction times as functions of foreperiod duration. *Journal of Experimental Psychology*, *69*, 382–386.

Holender, D., & Bertelson, P. (1975). Selective preparation and time uncertainty. *Acta Psychologica*, *39*(3), 193–203.

Hudson, T. E., Maloney, L. T., & Landy, M. S. (2007). Movement planning with probabilistic target information. *Journal of Neurophysiology*, *98*(5), 3034–3046.

Hudson, T. E., Maloney, L. T., & Landy, M. S. (2008). Optimal compensation for temporal uncertainty in movement planning. *PLoS Computational Biology*, *4*(7), e1000130.

Hyman, R. (1953). Stimulus information as a determinant of reaction time. *Journal of Experimental Psychology*, *45*(3), 188–196.

Ivry, R. B., & Richardson, T. C. (2002). Temporal control and coordination: the multiple timer model. *Brain and Cognition*, *48*(1), 117–132.

Ivry, R. B., & Schlerf, J. E. (2008). Dedicated and intrinsic models of time perception. *Trends in Cognitive Sciences*, *12*(7), 273–280.

Ivry, R. B., Spencer, R. M., Zelaznik, H. N., & Diedrichsen, J. (2002). The cerebellum and event timing. *Annals of the New York Academy of Sciences*, *978*, 302–317.

Jahanshahi, M., Brown, R. G., & Marsden, D. (1992). Simple and choice reaction time and the use of advance information for motor preparation in Parkinson's disease. *Brain*, *115*(2), 539 –564.

Jahanshahi, M., Jones, C. R. G., Dirnberger, G., & Frith, C. D. (2006). The substantia nigra pars compacta and temporal processing. *The Journal of Neuroscience*, *26*(47), 12266–12273.

Jahanshahi, M., Jones, C. R. G., Zijlmans, J., Katzenschlager, R., Lee, L., Quinn, N., Frith, C. D., et al. (2010). Dopaminergic modulation of striato-frontal connectivity during motor timing in Parkinson’s disease. *Brain*, *133*(3), 727–745.

Janssen, P., & Shadlen, M. N. (2005). A representation of the hazard rate of elapsed time in macaque area LIP. *Nature Neuroscience*, *8*(2), 234–241.

Jazayeri, M., & Shadlen, M. N. (2010). Temporal context calibrates interval timing. *Nature Neuroscience, 13*, 1020-1026.

Johnston, E. B., Cumming, B. G., & Landy, M. S. (1994). Integration of stereopsis and motion shape cues. *Vision Research*, *34*(17), 2259–2275.

Jones, C. R. G., & Jahanshahi, M. (2009a). The substantia nigra, the basal ganglia, dopamine and temporal processing. *Journal of Neural Transmission. Supplementum*, (73), 161–171.

Jones, C. R. G., & Jahanshahi, M. (2009b). The substantia nigra, the basal ganglia, dopamine and temporal processing. *Journal of Neural Transmission. Supplementum*, (73), 161–171.

Jones, C. R. G., Malone, T. J. L., Dirnberger, G., Edwards, M., & Jahanshahi, M. (2008). Basal ganglia, dopamine and temporal processing: performance on three timing tasks on and off medication in Parkinson’s disease. *Brain and Cognition*, *68*(1), 30–41.

Jones, C. R. G., Rosenkranz, K., Rothwell, J. C., & Jahanshahi, M. (2004). The right dorsolateral prefrontal cortex is essential in time reproduction: an investigation with repetitive transcranial magnetic stimulation. *Experimental Brain Research*, *158*(3), 366–372.

Jurkowski, A. J., Stepp, E., & Hackley, S. A. (2005). Variable foreperiod deficits in Parkinson's disease: dissociation across reflexive and voluntary behaviors. *Brain and Cognition*, *58*(1), 49–61.

Kacelnik, A., & Brunner, D. (2002). Timing and Foraging: Gibbon's Scalar Expectancy Theory and Optimal Patch Exploitation. *Learning and Motivation*, *33*(1), 177–195.

Kahneman, D., & Tversky, A. (1979). Prospect theory: An analysis of decision under risk. *Econometrica*, *47*(2), 263–292.

Kahneman, D., & Tversky, A. (1979). Prospect Theory: An Analysis of Decision under Risk. *Econometrica*, *47*(2), 263–291.

Kahneman, D., & Tversky, A. (2000). *Choices, Values, and Frames* (1st ed.). Cambridge University Press.

Kanai, R., Lloyd, H., Bueti, D., & Walsh, V. (2011). Modality-independent role of the primary auditory cortex in time estimation. *Experimental Brain Research, 209*(3), 465–471.

Keele, S. W., Pokorny, R. A., Corcos, D. M., & Ivry, R. (1985). Do perception and motor production share common timing mechanisms: a correctional analysis. *Acta Psychologica*, *60*(2-3), 173–191.

Klemmer, E. T. (1956). Time uncertainty in simple reaction time. *Journal of Experimental Psychology*, *51*(3), 179–184.

Klemmer, E. T. (1957). Simple reaction time as a function of time uncertainty. *Journal of Experimental Psychology*, *54*(3), 195–200.

Knill, D. C. (2007). Robust cue integration: a Bayesian model and evidence from cue-conflict studies with stereoscopic and figure cues to slant. *Journal of Vision*, *7*(7), 5.1–24.

Knill, D. C., & Saunders, J. A. (2003). Do humans optimally integrate stereo and texture information for judgments of surface slant? *Vision Research*, *43*(24), 2539–2558.

Koch, G., Costa, A., Brusa, L., Peppe, A., Gatto, I., Torriero, S., Gerfo, E. L., et al. (2008). Impaired reproduction of second but not millisecond time intervals in Parkinson's disease. *Neuropsychologia*, *46*(5), 1305–1313.

Körding, K. P., Beierholm, U., Ma, W. J., Quartz, S., Tenenbaum, J. B., & Shams, L. (2007). Causal inference in multisensory perception. *PloS One*, *2*(9), e943.

Körding, K. P., & Wolpert, D. M. (2004). Bayesian integration in sensorimotor learning. *Nature*, *427*(6971), 244–247.

Kujirai, T., Caramia, M. D., Rothwell, J. C., Day, B. L., Thompson, P. D., Ferbert, A., Wroe, S., et al. (1993). Corticocortical inhibition in human motor cortex. *The Journal of Physiology*, *471*, 501–519.

Lange, K. W., Tucha, O., Steup, A., Gsell, W., & Naumann, M. (1995). Subjective time estimation in Parkinson's disease. *Journal of Neural Transmission. Supplementum*, *46*, 433–438.

Leak, T. M., & Gibbon, J. (1995). Simultaneous timing of multiple intervals: implications of the scalar property. *Journal of Experimental Psychology. Animal Behavior Processes*, *21*(1), 3–19.

Lebedev, M. A., O'Doherty, J. E., & Nicolelis, M. A. L. (2008). Decoding of temporal intervals from cortical ensemble activity. *Journal of Neurophysiology*, *99*(1), 166–186.

Lejeune, H., & Wearden, J. H. (2006). Scalar properties in animal timing: conformity and violations. *Quarterly Journal of Experimental Psychology*, *59*(11), 1875–1908.

Leon, M. I., & Shadlen, M. N. (2003). Representation of time by neurons in the posterior parietal cortex of the macaque. *Neuron*, *38*(2), 317–327.

Levine, J. D., Funes, P., Dowse, H. B., & Hall, J. C. (2002). Resetting the circadian clock by social experience in Drosophila melanogaster. *Science*, *298*(5600), 2010–2012.

Lewis, P. A., & Miall, R. C. (2009). The precision of temporal judgement: milliseconds, many minutes, and beyond. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *364*(1525), 1897 –1905.

Lichtenstein, S., Slovic, P., Fischhoff, B., Layman, M., & Combs, B. (1978). Judged frequency of lethal events. *Journal of Experimental Psychology: Human Learning and Memory*, *4*(6), 511–578.

Livingston, S. C., & Ingersoll, C. D. (2008). Intra-rater reliability of transcranial magnetic stimulation technique to obtain motor evoked potentials. *International Journal of Neuroscience*, *118*(2), 239–256.

Los, S. A., & van den Heuvel, C. E. (2001). Intentional and unintentional contributions to nonspecific preparation during reaction time foreperiods. *Journal of Experimental Psychology. Human Perception and Performance*, *27*(2), 370–386.

Los, S., & Agter, F. (2005). Reweighting sequential effects across different distributions of foreperiods: segregating elementary contributions to nonspecific preparation. *Perception & Psychophysics*, *67*(7), 1161–1170.

Los, S., & Heslenfeld, D. (2005). Intentional and unintentional contributions to nonspecific preparation: electrophysiological evidence. *Journal of Experimental Psychology. General*, *134*(1), 52–72.

Los, S., Knol, D., & Boers, R. (2001). The foreperiod effect revisited: conditioning as a basis for nonspecific preparation. *Acta Psychologica*, *106*(1-2), 121–145.

Los, S., & Schut, M. (2008). The effective time course of preparation. *Cognitive Psychology*, *57*(1), 20–55.

Los, S. A. (2004). Inhibition of return and nonspecific preparation: separable inhibitory control mechanisms in space and time. *Perception & Psychophysics*, *66*(1), 119–130.

Los, S. A., & Horoufchin, H. (2011). Dissociative patterns of foreperiod effects in temporal discrimination and reaction time tasks. *Quarterly Journal of Experimental Psychology*, *64*(5), 1009–1020.

Macar, F., Coull, J., & Vidal, F. (2006). The supplementary motor area in motor and perceptual time processing: fMRI studies. *Cognitive Processing*, *7*(2), 89–94.

Mamassian, P. (2008). Overconfidence in an objective anticipatory motor task. *Psychological Science*, *19*(6), 601–606.

Mars, R. B., Bestmann, S., Rothwell, J. C., & Haggard, P. (2007). Effects of motor preparation and spatial attention on corticospinal excitability in a delayed-response paradigm. *Experimental Brain Research*, *182*(1), 125–129.

Mauk, M. D., & Buonomano, D. V. (2004). The neural basis of temporal processing. *Annual Review of Neuroscience*, *27*, 307–340.

McAuley, J. D., Miller, J. P., Wang, M., & Pang, K. C. H. (2010). Dividing time: concurrent timing of auditory and visual events by young and elderly adults. *Experimental Aging Research*, *36*(3), 306–324.

McCormick, D. A. (1989). GABA as an inhibitory neurotransmitter in human cerebral cortex. *Journal of Neurophysiology*, *62*(5), 1018–1027.

McCormick, D. A., & Williamson, A. (1989). Convergence and divergence of neurotransmitter action in human cerebral cortex. *Proceedings of the National Academy of Sciences of the United States of America*, *86*(20), 8098–8102.

McDonnell, M. N., Orekhov, Y., & Ziemann, U. (2006). The role of GABAB receptors in intracortical inhibition in the human motor cortex. *Experimental Brain Research*, *173*(1), 86–93.

Meck, W. H., & Church, R. M. (1984). Simultaneous temporal processing. *Journal of Experimental Psychology. Animal Behavior Processes*, *10*(1), 1–29.

Merchant, H., Luciana, M., Hooper, C., Majestic, S., & Tuite, P. (2007). Interval timing and Parkinson's disease: heterogeneity in temporal performance. *Experimental Brain Research*, *184*(2), 233–248.

Meredith, M. A., Nemitz, J. W., & Stein, B. E. (1987). Determinants of multisensory integration in superior colliculus neurons. I. Temporal factors. *The Journal of Neuroscience*, *7*(10), 3215–3229.

Meredith, M. A., & Stein, B. E. (1983). Interactions among converging sensory inputs in the superior colliculus. *Science*, *221*(4608), 389–391.

Meredith, M. A., & Stein, B. E. (1996). Spatial determinants of multisensory integration in cat superior colliculus neurons. *Journal of Neurophysiology*, *75*(5), 1843–1857.

Meulenbroek, R. G., & Van Galen, G. P. (1988). Foreperiod duration and the analysis of motor stages in a line-drawing task. *Acta Psychologica*, *69*(1), 19–34.

Michelet, T., Duncan, G. H., & Cisek, P. (2010). Response competition in the primary motor cortex: Corticospinal excitability reflects response replacement during simple decisions. *Journal of Neurophysiology, 104(1),* 119-127.

Miniussi, C., Wilding, E. L., Coull, J. T., & Nobre, A. C. (1999). Orienting attention in time. Modulation of brain potentials. *Brain*, *122 (8)*, 1507–1518.

Mita, A., Mushiake, H., Shima, K., Matsuzaka, Y., & Tanji, J. (2009). Interval time coding by neurons in the presupplementary and supplementary motor areas. *Nature Neuroscience*, *12*(4), 502–507.

Morse, D., & Sassone-Corsi, P. (2002). Time after time: inputs to and outputs from the mammalian circadian oscillators. *Trends in Neurosciences*, *25*(12), 632–637.

Muller, C. M. P., Brenner, E., & Smeets, J. B. J. (2009). Testing a counter-intuitive prediction of optimal cue combination. *Vision Research*, *49*(1), 134–139.

Niemi, R., & Naatanen, R. (1981). Foreperiod and Simple Reaction Time. *Psychological Bulletin*, *89*, 133–162.

Nobre, A., Correa, A., & Coull, J. (2007). The hazards of time. *Current Opinion in Neurobiology*, *17*(4), 465–470.

Orgs, G., Bestmann, S., Schuur, F., & Haggard, P. (2011). From body form to biological motion: the apparent velocity of human movement biases subjective time. *Psychological Science*, *22*(6), 712–717.

Oruç, I., Maloney, L. T., & Landy, M. S. (2003). Weighted linear cue combination with possibly correlated error. *Vision Research*, *43*(23), 2451–2468.

Parise, C. V., Spence, C., & Ernst, M. O. (2012). When Correlation Implies Causation in Multisensory Integration. *Current Biology, 22(1)*, 46-49.

Pastor, M. A., Artieda, J., Jahanshahi, M., & Obeso, J. A. (1992). Time estimation and reproduction is abnormal in Parkinson's disease. *Brain*, *115(1*), 211–225.

Piras, F., & Coull, J. T. (2011). Implicit, predictive timing draws upon the same scalar representation of time as explicit timing. *PloS One*, *6*(3), e18203.

Praamstra, P., Kourtis, D., Kwok, H. F., & Oostenveld, R. (2006). Neurophysiology of implicit timing in serial choice reaction-time performance. *The Journal of Neuroscience, 26*(20), 5448–5455.

Prut, Y., & Fetz, E. E. (1999). Primate spinal interneurons show pre-movement instructed delay activity. *Nature*, *401*(6753), 590–594.

Rakitin, B. C., Gibbon, J., Penney, T. B., Malapani, C., Hinton, S. C., & Meck, W. H. (1998). Scalar expectancy theory and peak-interval timing in humans. *Journal of Experimental Psychology. Animal Behavior Processes*, *24*(1), 15–33.

Rakow, T., Demes, K. A., & Newell, B. R. (2008). Biased samples not mode of presentation: Re-examining the apparent underweighting of rare events in experience-based choice. *Organizational Behavior and Human Decision Processes*, *106*(2), 168–179.

Rammsayer, T. H. (1993). On dopaminergic modulation of temporal information processing. *Biological Psychology*, *36*(3), 209–222.

Rammsayer, T. H. (1997). Are there dissociable roles of the mesostriatal and mesolimbocortical dopamine systems on temporal information processing in humans? *Neuropsychobiology*, *35*(1), 36–45.

Rammsayer, T. H. (1999). Neuropharmacological evidence for different timing mechanisms in humans. *The Quarterly Journal of Experimental Psychology. B, Comparative and Physiological Psychology*, *52*(3), 273–286.

Rammsayer, T. H., & Vogel, W. H. (1992). Pharmacologic properties of the internal clock underlying time perception in humans. *Neuropsychobiology*, *26*(1-2), 71–80.

Renoult, L., Roux, S., & Riehle, A. (2006). Time is a rubberband: neuronal activity in monkey motor cortex in relation to time estimation. *The European Journal of Neuroscience*, *23*(11), 3098–3108.

Reppert, S. M., & Weaver, D. R. (2002). Coordination of circadian timing in mammals. *Nature*, *418*(6901), 935–941.

Requin, J. (1969). Some data on neurophysiological processes involved in the preparatory motor activity to reaction time performance. *Acta Psychologica*, *30*, 358–367.

Requin, J., & Granjon, M. (1969). The effect of conditional probability of the response signal on the simple reaction time. *Acta Psychologica*, *31*, 129–144.

Reynolds, C., & Ashby, P. (1999). Inhibition in the human motor cortex is reduced just before a voluntary contraction. *Neurology*, *53*(4), 730–735.

Roesler, K. M., & Magistris, M. R. (2008). The size of motor-evoked potentials: influencing parameters and quantification. *The Oxford Handbook of Transcranial Magnetic Stimulation* (pp. 77–90). New York, USA: Oxford University Press.

Rohenkohl, G., Coull, J. T., & Nobre, A. C. (2011). Behavioural dissociation between exogenous and endogenous temporal orienting of attention. *PloS One*, *6*(1), e14620.

Rule, S. J. (1986). Subjective duration of simultaneous events. *Perception & Psychophysics*, *40*(1), 27–30.

Rushworth, M. F. S., Noonan, M. P., Boorman, E. D., Walton, M. E., & Behrens, T. E. (2011). Frontal cortex and reward-guided learning and decision-making. *Neuron*, *70*(6), 1054–1069.

Sakaba, T., & Neher, E. (2003). Direct modulation of synaptic vesicle priming by GABA(B) receptor activation at a glutamatergic synapse. *Nature*, *424*(6950), 775–778.

Sakai, K., Hikosaka, O., Takino, R., Miyauchi, S., Nielsen, M., & Tamada, T. (2000). What and when: parallel and convergent processing in motor control. *The Journal of Neuroscience*, *20*(7), 2691–2700.

Sanders, A. F. (1990). Issues and trends in the debate on discrete vs. continuous processing of information. *Acta Psychologica*, *74*(2-3), 123–167.

Sanger, T. D., Garg, R. R., & Chen, R. (2001). Interactions between two different inhibitory systems in the human motor cortex. *The Journal of Physiology*, *530*(2), 307–317.

Schirmer, A. (2004). Timing speech: a review of lesion and neuroimaging findings. *Brain Research. Cognitive Brain Research*, *21*(2), 269–287.

Schlerf, J. E., Spencer, R. M. C., Zelaznik, H. N., & Ivry, R. B. (2007). Timing of rhythmic movements in patients with cerebellar degeneration. *Cerebellum*, *6*(3), 221–231.

Schneider, D. W., & Anderson, J. R. (2011). A memory-based model of Hick's law. *Cognitive Psychology*, *62*(3), 193–222.

Seydell, A., McCann, B. C., Trommershäuser, J., & Knill, D. C. (2008). Learning stochastic reward distributions in a speeded pointing task. *The Journal of Neuroscience, 28*(17), 4356–4367.

Shih, L. Y. L., Kuo, W.-J., Yeh, T.-C., Tzeng, O. J. L., & Hsieh, J.-C. (2009). Common neural mechanisms for explicit timing in the sub-second range. *Neuroreport*, *20*(10), 897–901.

Sinclair, C., & Hammond, G. R. (2008). Reduced intracortical inhibition during the foreperiod of a warned reaction time task. *Experimental Brain Research, 186*(3), 385–392.

Sinclair, C., & Hammond, G. R. (2009). Excitatory and inhibitory processes in primary motor cortex during the foreperiod of a warned reaction time task are unrelated to response expectancy. *Experimental Brain Research, 194*(1), 103–113.

Smith, J. G., Harper, D. N., Gittings, D., & Abernethy, D. (2007). The effect of Parkinson's disease on time estimation as a function of stimulus duration range and modality. *Brain and Cognition*, *64*(2), 130–143.

Smyrnis, N., Karantinos, T., Malogiannis, I., Theleritis, C., Mantas, A., Stefanis, N. C., Hatzimanolis, J., et al. (2009). Larger variability of saccadic reaction times in schizophrenia patients. *Psychiatry Research*, *168*(2), 129–136.

Sober, S. J., & Sabes, P. N. (2005). Flexible strategies for sensory integration during motor planning. *Nature Neuroscience*, *8*(4), 490–497.

Sohn, M.-H., & Carlson, R. A. (2003). Implicit temporal tuning of working memory strategy during cognitive skill acquisition. *The American Journal of Psychology*, *116*(2), 239–256.

Sohn, Y. H., Wiltz, K., & Hallett, M. (2002). Effect of volitional inhibition on cortical inhibitory mechanisms. *Journal of Neurophysiology*, *88*(1), 333–338.

Soto, O., Valls-Sole, J., & Kumru, H. (2010). Paired-Pulse Transcranial Magnetic Stimulation During Preparation for Simple and Choice Reaction Time Tasks. *J Neurophysiol*, *104*(3), 1392–1400.

Spijkers, W. A. C. (1990). The relation between response-specificity, S-R compatibility, foreperiod duration and muscle-tension in a target aiming task. *Acta Psychologica*, *75*(3), 261–277.

Spijkers, W. A. C., & Walter, A. (1985). Response processing stages in choice reactions. *Acta Psychologica*, *58*(2), 191–204.

Staddon, J. E. R. (2005). Interval timing: memory, not a clock. *Trends in Cognitive Sciences*, *9*(7), 312–314.

Steinborn, M. B., Rolke, B., Bratzke, D., & Ulrich, R. (2008). Sequential effects within a short foreperiod context: evidence for the conditioning account of temporal preparation. *Acta Psychologica*, *129*(2), 297–307.

Takei, T., Hashimoto, T., Hagura, N., Matsumura, M., & Naito, E. (2005). Reduction of cortico-spinal excitability by transcranial magnetic stimulation at predictable timing. *The Japanese Journal of Physiology*, *55*(2), 93–99.

Tandonnet, C., Burle, B., Vidal, F., & Hasbroucq, T. (2003). The influence of time preparation on motor processes assessed by surface Laplacian estimation. *Clinical Neurophysiology*, *114*(12), 2376–2384.

Teki, S., Grube, M., Kumar, S., & Griffiths, T. D. (2011). Distinct neural substrates of duration-based and beat-based auditory timing. *The Journal of Neuroscience*, *31*(10), 3805–3812.

Thaut, M. H., Stephan, K. M., Wunderlich, G., Schicks, W., Tellmann, L., Herzog, H., McIntosh, G. C., et al. (2009). Distinct cortico-cerebellar activations in rhythmic auditory motor synchronization. *Cortex*, *45*(1), 44–53.

Treisman, M. (1963). Temporal discrimination and the indifference interval: Implications for a model of the "internal clock." *Psychological Monographs: General and Applied*, *77*(13), 1–31.

Trepel, C., Fox, C. R., & Poldrack, R. A. (2005). Prospect theory on the brain? Toward a cognitive neuroscience of decision under risk. *Brain Research. Cognitive Brain Research*, *23*(1), 34–50.

Trillenberg, P., Verleger, R., Wascher, E., Wauschkuhn, B., & Wessel, K. (2000). CNV and temporal uncertainty with "ageing" and "non-ageing" S1-S2 intervals. *Clinical Neurophysiology*, *111*(7), 1216–1226.

Trommershäuser, J. (2009). Biases and optimality of sensory-motor and cognitive decisions. *Progress in Brain Research*, *174*, 267–278.

Trommershäuser, J., Gepshtein, S., Maloney, L. T., Landy, M. S., & Banks, M. S. (2005). Optimal compensation for changes in task-relevant movement variability. *The Journal of Neuroscience*, *25*(31), 7169–7178.

Trommershäuser, J., Landy, M. S., & Maloney, L. T. (2006). Humans rapidly estimate expected gain in movement planning. *Psychological Science*, *17*(11), 981–988.

Trommershäuser, J., Maloney, L. T., & Landy, M. S. (2003). Statistical decision theory and trade-offs in the control of motor response. *Spatial Vision*, *16*(3-4), 255–275.

Trommershäuser, J., Maloney, L. T., & Landy, M. S. (2008). Decision making, movement planning and statistical decision theory. *Trends in Cognitive Sciences*, *12*(8), 291–297.

Turgeon, M., Wing, A. M., & Taylor, L. W. (2011). Timing and aging: slowing of fastest regular tapping rate with preserved timing error detection and correction. *Psychology and Aging*, *26*(1), 150–161.

Tversky, A., & Kahneman, D. (1992). Advances in prospect theory: cumulative representation of uncertainty. *Journal of Risk and Uncertainty*, *5*, 297–323.

Ulrich, R., Nitschke, J., & Rammsayer, T. (2006). Crossmodal temporal discrimination: assessing the predictions of a general pacemaker-counter model. *Perception & Psychophysics*, *68*(7), 1140–1152.

Vallesi, A., McIntosh, A. R., Shallice, T., & Stuss, D. T. (2009). When time shapes behavior: fMRI evidence of brain correlates of temporal monitoring. *Journal of Cognitive Neuroscience*, *21*(6), 1116–1126.

Vallesi, A., Mussoni, A., Mondani, M., Budai, R., Skrap, M., & Shallice, T. (2007). The neural basis of temporal preparation: Insights from brain tumor patients. *Neuropsychologia*, *45*(12), 2755–2763.

Vallesi, A., & Shallice, T. (2007). Developmental dissociations of preparation over time: deconstructing the variable foreperiod phenomena. *Journal of Experimental Psychology. Human Perception and Performance*, *33*(6), 1377–1388.

Vallesi, A., Shallice, T., & Walsh, V. (2007). Role of the prefrontal cortex in the foreperiod effect: TMS evidence for dual mechanisms in temporal preparation. *Cerebral Cortex*, *17*(2), 466–474.

van Beers, R. J., Baraduc, P., & Wolpert, D. M. (2002). Role of uncertainty in sensorimotor control. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *357*(1424), 1137–1145.

van Beers, R. J., Wolpert, D. M., & Haggard, P. (2002). When feeling is more important than seeing in sensorimotor adaptation. *Current Biology*, *12*(10), 834–837.

Van der Lubbe, R. H. J., Los, S. A., Jaśkowski, P., & Verleger, R. (2004). Being prepared on time: on the importance of the previous foreperiod to current preparation, as reflected in speed, force and preparation-related brain potentials. *Acta Psychologica*, *116*(3), 245–262.

van Elswijk, G., Kleine, B. U., Overeem, S., & Stegeman, D. F. (2007). Expectancy induces dynamic modulation of corticospinal excitability. *Journal of Cognitive Neuroscience*, *19*(1), 121–131.

van Elswijk, G., Schot, W. D., Stegeman, D. F., & Overeem, S. (2008). Changes in corticospinal excitability and the direction of evoked movements during motor preparation: a TMS study. *BMC Neuroscience*, *9*: 51.

Vicario, C. M., Bonní, S., & Koch, G. (2011). Left hand dominance affects supra-second time processing. *Frontiers in Integrative Neuroscience*, *5*: 65.

Wagle-Shukla, A., Ni, Z., Gunraj, C. A., Bahl, N., & Chen, R. (2009). Effects of short interval intracortical inhibition and intracortical facilitation on short interval intracortical facilitation in human primary motor cortex. *The Journal of Physiology*, *587*(23), 5665–5678.

Walsh, V., & Cowey, A. (1998). Magnetic stimulation studies of visual cognition. *Trends in Cognitive Sciences*, *2*(3), 103–110.

Wearden, J. H., Smith-Spark, J. H., Cousins, R., Edelstyn, N. M. J., Cody, F. W. J., & O'Boyle, D. J. (2008). Stimulus timing by people with Parkinson's disease. *Brain and Cognition*, *67*(3), 264–279.

Weisswange, T. H., Rothkopf, C. A., Rodemann, T., & Triesch, J. (2011). Bayesian cue integration as a developmental outcome of reward mediated learning. *PloS One*, *6*(7), e21575.

Welch, R. B., & Warren, D. H. (1980). Immediate perceptual response to intersensory discrepancy. *Psychological Bulletin*, *88*(3), 638–667.

Wencil, E. B., Coslett, H. B., Aguirre, G. K., & Chatterjee, A. (2010). Carving the clock at its component joints: neural bases for interval timing. *Journal of Neurophysiology*, *104*(1), 160–168.

Wiener, M., Turkeltaub, P., & Coslett, H. B. (2010). The image of time: A voxel-wise meta-analysis. *NeuroImage*, *49*(2), 1728–1740.

Wing, A. M., Doumas, M., & Welchman, A. E. (2010). Combining multisensory temporal information for movement synchronisation. *Experimental Brain Research*, *200*(3-4), 277–282.

Wing, A. M., & Kristofferson, A. B. (1973). The timing of interresponse intervals. *Perception & Psychophysics*, *13*(3), 455–460.

Wittmann, M. (2011). Moments in time. *Frontiers in Integrative Neuroscience*, *5*: 66.

Wolpert, D. M. (2007). Probabilistic models in human sensorimotor control. *Human Movement Science*, *26*(4), 511–524.

Woodrow, H. (1914). The measurement of attention. *Psychological Monographs*, *17*(5).

Zahn, T. P., & Rosenthal, D. (1966). Simple reaction time as a function of the relative frequency of the preparatory interval. *Journal of Experimental Psychology*, *72*(1), 15–19.

Ziemann, U., Rothwell, J. C., & Ridding, M. C. (1996). Interaction between intracortical inhibition and facilitation in human motor cortex. *The Journal of Physiology*, *496 (3)*, 873–881.

Ziemann, U., Tergau, F., Wassermann, E. M., Wischer, S., Hildebrandt, J., & Paulus, W. (1998). Demonstration of facilitatory I wave interaction in the human motor cortex by paired transcranial magnetic stimulation. *The Journal of Physiology*, *511 (1)*, 181–190.