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The Neural Correlates of Time: A Meta-analysis of Neuroimaging Studies

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Abstract

■ During the last two decades, our inner sense of time has been repeatedly studied with the help of neuroimaging techniques. These investigations have suggested the specific involvement of different brain areas in temporal processing. At least two distinct neural systems are likely to play a role in measuring time: One is mainly constituted by subcortical structures and is supposed to be more related to the estimation of time intervals below the 1-sec range (subsecond timing tasks), and the other is mainly constituted by cortical areas and is supposed to be more related to the estimation of time intervals above the 1-sec range (suprasecond timing tasks). Tasks can then be performed in motor or nonmotor (perceptual) conditions, thus providing four different categories of time processing. Our

meta-analytical investigation partly confirms the findings of previous meta-analytical works. Both sub- and suprasecond tasks recruit cortical and subcortical areas, but subcortical areas are more intensely activated in subsecond tasks than in supra-second tasks, which instead receive more contributions from cortical activations. All the conditions, however, show strong activations in the SMA, whose rostral and caudal parts have an important role not only in the discrimination of different time intervals but also in relation to the nature of the task conditions. This area, along with the striatum (especially the putamen) and the claustrum, is supposed to be an essential node in the different networks engaged when the brain creates our sense of time. ■

INTRODUCTION

The passage of time is one of the most pervasive aspects of our lives. Intuitively, everyone feels to know what it means that time passes, but if we were asked to express in words the nature of time and the feeling of temporality, we would be in the same situation as Saint Augustine, who declared in his *Confessions*: “What then is time? If no one asks me, I know what it is. If I wish to explain it to him who asks, I do not know.” Saint Augustine wrote between the IV and V centuries AD, but to date the nature of time remains elusive. Time has been considered an essential feature of reality, on the one hand (Unger & Smolin, 2015), or a figment of the way we know reality, on the other (Rovelli, 2018). Independent of the fact that time is a real constituent of the outside world or just a fabrication of our inner world, the brain is unquestionably involved in perceiving or constructing the temporal framework within which events (seem to) happen and interact.

During the last two decades, time perception (or construction) has been repeatedly investigated with the help of neuroimaging techniques. These studies have put forward different results, which in turn have been used to support different theories about the involvement

of specific brain areas in temporal processing. These theories can be divided into two types: dedicated and intrinsic models (Ivry & Schlerf, 2008). The dedicated models hypothesize a specific mechanism exclusively devoted to the estimation of time; in contrast, the intrinsic models assume that various brain structures normally associated with sensory and cognitive processes can also act as interval timers (Wittmann, 2013). A classic example of a dedicated mechanism for time perception is the pacemaker-accumulator system (Taatgen, van Rijn, & Anderson, 2007; Zakay & Block, 1997). The idea is that the neural pacemaker generates a series of pulses that, just like the ticks of a clock, are recorded to measure time intervals. In particular, the dopaminergic system and the BG, especially the striatum (caudate nucleus and putamen) and the substantia nigra pars compacta, are thought to be the underpinnings of this neural pacemaker (Meck, Penney, & Pouthas, 2008; Buhusi & Meck, 2005). In particular, the striatum, which receives inputs from a large number of cortical neurons, would be the main region involved in detecting the oscillatory patterns or frequencies related to the activity of different cortical sites. Neuroimaging investigations that applied different techniques (fMRI, PET) have supported the pivotal role played by the striatum in time processing (Harrington, Zimelman, Hinton, & Rao, 2010; Coull & Nobre, 2008; Rao, Mayer, & Harrington, 2001). However, other experiments provide evidence that, according to different tasks

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and conditions, other several brain areas are supposed to be involved in the perception of time.

Various mechanisms underlying intrinsic models have therefore been proposed. The most general mechanism assumes that short-term synaptic plasticity, which is at the basis of the dynamics of neural states, can transform the brain networks in time keepers (Buonomano & Maass, 2009). According to this view, every cerebral area has the capacity to process and estimate time. Other proposals, on the contrary, are more specific and pinpoint a certain brain region or neural population as the substrate of a particular temporal task. For instance, the right pFC (Lewis & Miall, 2006a, 2006b), the cerebellum (Ivry, Spencer, Zelaznik, & Diedrichsen, 2002), the SMA (Macar, Coull, & Vidal, 2006), the right inferior parietal lobule (Battelli, Pascual-Leone, & Cavanagh, 2007), and the anterior insula (Craig, 2009a) have been variously associated with time perception, judgment, and the processing of intervals' duration.

The variegated picture of our inner sense of time created by the involvement of these various brain structures is probably due to different experimental contexts and settings, the characteristics of the tasks employed, the duration of stimuli, the nature of responses, as well as the application of different statistical procedures. For example, Lewis and Miall (2003a) carried out a label-based review of neuroimaging studies on time perception. The authors divided the experimental results according to the interval duration (i.e., subsecond or suprasedond tasks), the use of movement (i.e., motor or nonmotor tasks) and the nature of response (i.e., automatic or cognitively controlled tasks).

With regard to motor timing research, the task that is most frequently used is paced finger tapping: Participants are asked to tap a key following the rhythm of an isochronous metronome and then continue tapping at the same pace in absence of stimulation. In some experiments, the continuation phase is not required, but the participants are asked to tap at the middle point between groups of pacing stimuli. Other nonmotor experiments use the interval reproduction task, in which participants recall the duration of an interval between two stimuli to which they were previously exposed. A variation of this task is to ask the participants directly, without exposure, to produce a specific interval (i.e., "produce an interval of 6 sec"). On the other hand, time perception tasks require participants to judge the span of intervals. Frequently, participants are asked to compare and discriminate the duration of two successive stimuli by judging which of them is longer than the other. In these experiments, the duration of the stimuli to be judged is very variable, ranging from 200 to 24 sec. According to these different timing tasks, different brain structures are recruited (Buhusi & Meck, 2005; Mauk & Buonomano, 2004; Lewis & Miall, 2003a). Furthermore, neuropsychological studies in humans and research on animals point out that the estimation of temporal intervals above and below 1 sec relies on the activation of different

neural mechanisms and assemblies (Harrington & Haaland, 1999; Gibbon, Malapani, Dale, & Gallistel, 1997).

Overall, with regard to these different experimental conditions, studies have suggested that at least two distinct neural systems are likely to play a role in measuring time: One is mainly constituted by subcortical structures and is supposed to be more related to subsecond timing tasks, and the other is mainly constituted by cortical areas and is supposed to be more related to suprasedond timing tasks.

The distinction between different tasks and time intervals has been also highlighted by the meta-analysis of Wiener, Turkeltaub, and Coslett (2010), which analyzed four different conditions: subsecond motor, subsecond perceptual (i.e., nonmotor), suprasedond motor, and suprasedond perceptual. We have decided to adhere to this distinction, as it describes better the current literature on time perception studies. It should be observed, however, that it has some limitations, especially with regard to the category of the "perceptual" condition. In fact, rigorously speaking, this category is not strictly perceptual, as its experimental tasks include also the engagement of higher order cognitive functions, such as attention and salience. As Wiener et al. (2010), we use therefore "perceptual" in a broad sense as a synonym of "nonmotor," so as to designate all the experiments in which the task requirement is not strictly motor. For the studies that tested an interval across subsecond and suprasedond stimuli, we also decided, like Wiener et al. (2010), to determine whether most of the interval was above or below 1 sec and attribute them to the corresponding category. Furthermore, with regard to these possible confounding factors, we applied the fail-safe technique to assess the robustness of our results (see Methods for a detailed explanation of this procedure).

The results of the meta-analysis by Wiener et al. (2010) supported the idea that certain neural structures are involved in subsecond timing tasks and others in suprasedond timing tasks. In particular, the analysis of subsecond tasks revealed a greater activation of subcortical sites, such as the bilateral cerebellum and left BG. In contrast, the analysis of suprasedond tasks principally showed the activations of cortical areas, such as the bilateral SMA, frontal cortex, and cingulate gyri. Similarly, the meta-analysis carried out by Ortuño, Guillen-Grima, Lopez-Garcia, Gomez, and Pla (2011) largely reproduced these findings. However, in this case statistical analyses were performed on independent studies and only considered the cerebral activations related to implicit or explicit time estimation tasks. Finally, Schwartze, Rothermich, and Kotz (2012) focused their meta-analysis of fMRI studies on a subarea of the SMA by contrasting different temporal processing functions, such as sensory, sensorimotor, sequential, nonsequential, explicit, nonexplicit, subsecond, or suprasedond tasks. These authors identified different activations of the SMA, which might be correlated with different types of temporal processing.

Table 1. Articles Included in the Meta-analysis Using the PRISMA Statement International Guidelines

| <i>Study</i> | <i>Tool</i> | <i>Participants</i> | <i>Foci</i> | <i>Experimental Task (Contrast or Condition)</i> | <i>Duration (msec)</i> |
|--------------------------------------|-------------|---------------------|-------------|--|------------------------|
| Aso et al. (2010) (Exp. A) | fMRI | 14 | 6 | Temporal reproduction (main effect of motor timing) | 500–999 |
| Bengtsson et al. (2005) | fMRI | 7 | 6 | Paced finger tapping and articulation (more vs. less complex) | 375–750–1125 |
| Bueti, Walsh, et al. (2008) (Exp. A) | fMRI | 14 | 11 | Temporal reproduction (action vs. control) | 300–600–900–1200 |
| Berns et al. (1997) | PET | 10 | 3 | RT sequence (more vs. less complex) | 700 |
| Jahanshahi et al. (2006) (Exp. A) | PET | 8 | 11 | Temporal reproduction (short vs. long intervals) | 500 |
| Jancke et al. (2000) | fMRI | 8 | 3 | Paced finger tapping (paced vs. cued finger) | 400 |
| Jantzen et al. (2004) | fMRI | 14 | 10 | Paced finger tapping (syncopation vs. synchronization) | 800 |
| Jantzen et al. (2005) | fMRI | 12 | 7 | Paced finger tapping (syncopation vs. synchronization) | 800 |
| Jantzen et al. (2007) | fMRI | 9 | 7 | Paced finger tapping (paced vs. cued finger) | 800 |
| Karabanov et al. (2009) | fMRI | 16 | 43 | Temporal sequence performance (visual vs. auditory rhythms) | 375–750–1125–1500 |
| Lewis et al. (2004) | fMRI | 10 | 42 | Paced finger tapping (paced vs. cued finger) | 700 |
| Lutz et al. (2000) | fMRI | 14 | 1 | Paced finger tapping (isochronous vs. nonisochronous) | 667 |
| Mayville et al. (2002) | fMRI | 9 | 20 | Paced finger tapping (syncopation vs. synchronization) | 800 |
| Murai & Yotsumoto (2016) (Exp. A) | fMRI | 21 | 7 | Temporal duration reproduction (sub vs. suprasedond) | 400 |
| Ortuño et al. (2002) | PET | 10 | 9 | Temporal articulation (mentally vs. auditory rhythm counting) | 1000 |
| Oullier et al. (2005) (Exp. A) | fMRI | 15 | 19 | Paced finger tapping (syncopation vs. synchronization) | 800 |
| Oullier et al. (2005) (Exp. B) | fMRI | 15 | 12 | Paced finger tapping (synchronization vs. syncopation) | 800 |
| Pastor et al. (2004) | fMRI | 14 | 6 | Temporal discrimination (clicks vs. location) | 5–140 |
| Penhune et al. (1998) (Exp. A) | PET | 11 | 5 | Paced finger tapping (novel vs. learned) | 250 |
| Penhune et al. (1998) (Exp. B) | PET | 11 | 4 | Paced finger tapping (novel vs. learned) | 750 |
| Pope et al. (2005) | fMRI | 13 | 21 | Temporal sequences reproduction (main effect of alternating force) | 400–800 |
| Rao et al. (1997) (Exp. A) | fMRI | 13 | 7 | Temporal discrimination (temporal continuation vs. pitch) | 300 |

Table 1. (continued)

| <i>Study</i> | <i>Tool</i> | <i>Participants</i> | <i>Foci</i> | <i>Experimental Task (Contrast or Condition)</i> | <i>Duration (msec)</i> |
|--|-------------|---------------------|-------------|---|------------------------|
| Rao et al. (1997) (Exp. B) | fMRI | 13 | 7 | Temporal discrimination (temporal continuation vs. pitch) | 600 |
| Schubotz & von Cramon (2001) (Exp. A) | fMRI | 12 | 20 | Temporal reproduction (temporal vs. control pressing) | 290–1450 |
| <i>Subsecond motor timing condition: 21 articles, 24 experiments, 293 participants, and 287 foci of activation</i> | | | | | |
| Aso et al. (2010) (Exp. B) | fMRI | 14 | 4 | Temporal discrimination (main effect for sensory timing) | 500–999 |
| Bengtsson et al. (2009) (Exp. A) | fMRI | 17 | 12 | Auditory rhythm perception (rhythm vs. random) | 200–400–600–800 |
| Bengtsson et al. (2009) (Exp. B) | fMRI | 17 | 7 | Auditory rhythm perception (metric vs. isochronous) | 200–300–700–900 |
| Beudel et al. (2009) (Exp. A) | fMRI | 18 | 10 | Temporal estimation (time ahead vs. stop) | 100–800 |
| Beudel et al. (2009) (Exp. B) | fMRI | 18 | 9 | Temporal estimation (time ahead vs. spatial place) | 100–800 |
| Bueti, Walsh, et al. (2008) (Exp. B) | fMRI | 14 | 4 | Temporal estimation (perception vs. control) | 300–600–900–1200 |
| Coull & Nobre (1998) (Exp. A) | PET | 15 | 4 | Temporal perception (when vs. where) | 0–315 |
| Coull & Nobre (1998) (Exp. B) | fMRI | 15 | 3 | Temporal perception (when vs. where) | 0–315 |
| Ferrandez et al. (2003) | fMRI | 11 | 12 | Temporal discrimination (estimation vs. intensity of duration) | 700 |
| Gutyrcchik et al. (2010) | fMRI | 13 | 2 | Temporal perception (duration vs. color) | 100–250–1000–1300 |
| Lewis & Miall (2003b) (Exp. A) | fMRI | 8 | 20 | Temporal discrimination (temporal vs. length) | 600 |
| Maquet et al. (1996) | PET | 9 | 6 | Temporal discrimination (time vs. intensity duration) | 700 |
| Mathiak et al. (2004) | fMRI | 12 | 1 | Temporal auditory discrimination (auditory tones duration) | 200 |
| Neufang et al. (2008) | fMRI | 34 | 1 | Temporal discrimination (time vs. visual compatibility) | 250–350 |
| Schubotz et al. (2000) | fMRI | 20 | 14 | Temporal discrimination (temporal vs. color pitch) | 900 |
| Schubotz & von Cramon (2001) (Exp. B) | fMRI | 12 | 20 | Temporal monitoring (temporal vs. control monitoring) | 290–1450 |
| Shih et al. (2009) | fMRI | 17 | 5 | Temporal discrimination (temporal vs. control) | 100–450 |
| Shih et al. (2010) | fMRI | 21 | 13 | Temporal discrimination (temporal vs. control) | 400–450 |
| Tipples et al. (2013) | fMRI | 17 | 8 | Temporal estimation (duration vs. gender of stimuli) | 400–700–1000–1300–1600 |
| Tomasi et al. (2015) | fMRI | 36 | 27 | Temporal prediction (temporal vs.) | 600 |

Table 1. (continued)

| <i>Study</i> | <i>Tool</i> | <i>Participants</i> | <i>Foci</i> | <i>Experimental Task (Contrast or Condition)</i> | <i>Duration (msec)</i> |
|--|-------------|---------------------|-------------|---|------------------------|
| | | | | memory attention) | |
| Tregellas et al. (2006) | fMRI | 20 | 10 | Temporal discrimination (difficult vs. easy) | 200 |
| van Wassenhove et al. (2011) (Exp. A) | fMRI | 15 | 6 | Temporal dilation estimation (looming vs. standard stimuli) | 500 |
| van Wassenhove et al. (2011) (Exp. B) | fMRI | 15 | 8 | Temporal dilation estimation (receding vs. standard stimuli) | 500 |
| Wittmann, van Wassenhove, et al. (2010) (Exp. A) | fMRI | 20 | 6 | Temporal dilation estimation (looming vs. standard stimuli) | 500 |
| Wittmann, van Wassenhove, et al. (2010) (Exp. B) | fMRI | 20 | 8 | Temporal dilation estimation (receding vs. standard stimuli) | 500 |
| <i>Subsecond perceptual (nonmotor) timing condition: 20 articles, 25 experiments, 428 participants, and 220 foci of activation</i> | | | | | |
| Ackermann et al. (2001) | fMRI | 8 | 9 | Paced finger tapping (isochronous trains of clicks at different frequencies) | 6000 |
| Basso et al. (2003) | fMRI | 5 | 8 | Temporal production (time vs. working memory control) | 1500 |
| Botzung et al. (2008) (Exp. A) | fMRI | 10 | 11 | Events evocation (past vs. semantic memory condition) | 3700–11240 |
| Botzung et al. (2008) (Exp. B) | fMRI | 10 | 12 | Events evocation (future vs. semantic memory condition) | 3700–11240 |
| Brunia et al. (2000) | PET | 8 | 4 | Temporal production (correct vs. incorrect feedback) | 3000 |
| Coull et al. (2013) (Exp. A) | fMRI | 27 | 22 | Temporal production (temporal vs. neutral reproduction) | 600–1000–1400 |
| Dudukovic & Wagner (2007) | fMRI | 18 | 11 | Temporal decision (recent vs. new stimuli) | 5000 |
| Garraux et al. (2005) | fMRI | 11 | 1 | Paced finger tapping (timing vs. order) | 2000 |
| Jahanshahi et al. (2006) (Exp. B) | PET | 8 | 14 | Temporal reproduction (long vs. short intervals) | 2000 |
| Jech et al. (2005) | fMRI | 9 | 4 | Temporal reproduction (increase in duration length) | 500-16800 |
| Kawashima et al. (2000) | fMRI | 8 | 4 | Paced finger tapping (paced vs. cued finger) | 1500 |
| Knutson et al. (2004) | fMRI | 19 | 7 | Temporal order (script vs. chronological order) | 2500 |
| Larsson et al. (1996) | fMRI | 8 | 4 | Paced finger tapping (paced vs. cued finger) | 3800 |
| Lejeune et al. (1997) | PET | 12 | 4 | Paced finger tapping (paced vs. cued finger) | 2700 |
| Lewis & Miall (2002) | fMRI | 8 | 9 | Temporal reproduction (reproduction vs. control pressing) | 3000 |
| Macar et al. (2002) | PET | 15 | 6 | Temporal reproduction (temporal vs. control pressing) | 2200–3200–9000-13000 |
| Macar et al. (2004) | fMRI | 13 | 2 | Temporal reproduction | 2500 |

Table 1. (continued)

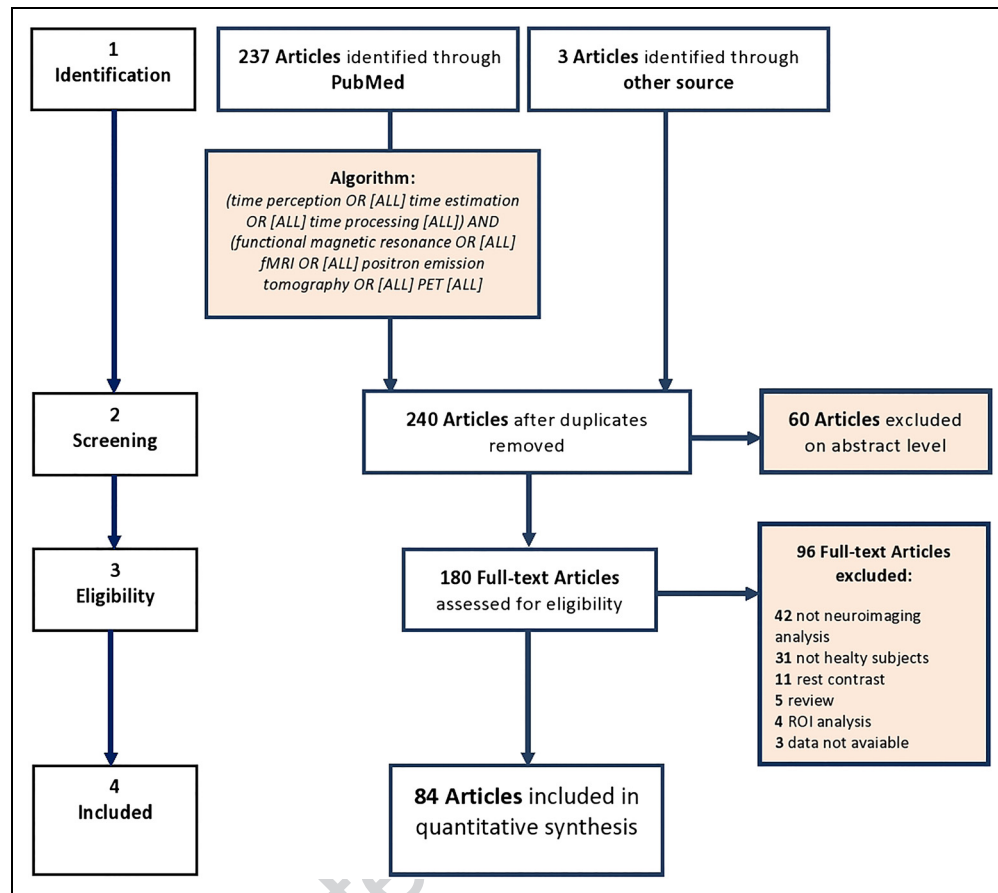
| <i>Study</i> | <i>Tool</i> | <i>Participants</i> | <i>Foci</i> | <i>Experimental Task (Contrast or Condition)</i> | <i>Duration (msec)</i> |
|--|-------------|---------------------|-------------|--|------------------------|
| | | | | (temporal vs. force) | |
| Murai & Yotsumoto (2016) (Exp. B) | fMRI | 21 | 16 | Temporal duration reproduction (supra vs. subsecond) | 2500 |
| Rekkas et al. (2005) (Exp. A) | fMRI | 10 | 3 | Temporal discrimination (semantic temporal order vs. spatial location) | 6000 |
| Rekkas et al. (2005) (Exp. B) | fMRI | 10 | 5 | Temporal discrimination (autobiographic temporal order vs. spatial location) | 6000 |
| Riecker et al. (2003) | fMRI | 8 | 8 | Paced finger tapping (isochronous trains of clicks at different frequencies) | 6000 |
| Riecker et al. (2006) | fMRI | 8 | 13 | Paced finger tapping (self-paced syllable repetition at different frequencies) | 6000 |
| Rubia et al. (1998) | fMRI | 6 | 4 | Paced finger tapping (high- vs. low-frequency synchronization) | 3000 |
| Shergill et al. (2006) | fMRI | 8 | 9 | Temporal articulation (paced vs. cued) | 2000 |
| Stevens et al. (2007) | fMRI | 31 | 12 | Paced finger tapping (syncopation vs. synchronization) | 750–1500–3500 |
| Taniwaki et al. (2006) | fMRI | 12 | 16 | Temporal execution (self-initiated vs. externally triggered movements) | 40000 |
| Teki & Griffiths (2016) | fMRI | 19 | 9 | Temporal reproduction (temporal vs. control) | 1500–2000 |
| Tracy et al. (2000) | fMRI | 6 | 3 | Temporal production (duration reproduction at different intervals) | 1200–2400 |
| Wittmann, Simmons, et al. (2010) (Exp. A) | fMRI | 14 | 3 | Temporal reproduction (temporal vs. control) | 3000 |
| Wittmann, Simmons, et al. (2010) (Exp. B) | fMRI | 14 | 7 | Temporal reproduction (temporal vs. control) | 9000 |
| Wittmann, Simmons, et al. (2010) (Exp. C) | fMRI | 14 | 3 | Temporal reproduction (temporal vs. control) | 18000 |
| Wittmann et al. (2011) (Exp. A) | fMRI | 27 | 8 | Temporal reproduction (temporal vs. control) | 3000 |
| Wittmann et al. (2011) (Exp. B) | fMRI | 27 | 4 | Temporal reproduction (temporal vs. control) | 9000 |
| Wittmann et al. (2011) (Exp. C) | fMRI | 27 | 6 | Temporal reproduction (temporal vs. control) | 18000 |
| <i>Suprasecond motor timing condition: 28 articles, 34 experiments, 459 participants, and 261 foci of activation</i> | | | | | |
| Apaydin et al. (2018) | fMRI | 18 | 9 | Temporal perception (time vs. reward) | 2500 |
| Carvalho et al. (2016) (Exp. A) | fMRI | 16 | 16 | Temporal expectation (nonperiodic vs. periodic) | 1340–2000 |
| Carvalho et al. (2016) (Exp. B) | fMRI | 16 | 7 | Temporal expectation (nonperiodic vs. periodic) | 1340–2000 |
| Coull et al. (2000) | fMRI | 6 | 18 | Temporal estimation (long vs. short target presentation) | 600–1400 |
| Coull et al. (2004) | fMRI | 12 | 10 | Temporal discrimination (increase | 540–1080–1620 |

Table 1. (continued)

| <i>Study</i> | <i>Tool</i> | <i>Participants</i> | <i>Foci</i> | <i>Experimental Task (Contrast or Condition)</i> | <i>Duration (msec)</i> |
|-----------------------------------|-------------|---------------------|-------------|--|------------------------|
| | | | | in attention to time) | |
| Coull et al. (2013) (Exp. B) | fMRI | 27 | 15 | Temporal prediction (temporal vs. neutral orienting) | 600–1000–1400 |
| Dirnberger et al. (2012) | fMRI | 7 | 7 | Incorrect time estimation (aversive vs. neutral context) | 1800–2200 |
| Harrington et al. (2004) | fMRI | 24 | 26 | Temporal duration discrimination (main effect of encoding) | 1200–1800 |
| Harrington et al. (2010) | fMRI | 20 | 7 | Temporal duration discrimination (time vs. pitch) | 10000–12500 |
| Herrmann et al. (2014) | fMRI | 19 | 5 | Temporal rate change perception (sound vs. silent trials) | 6400 |
| Jueptner et al. (1996) | fMRI | 6 | 6 | Temporal discrimination (temporal vs. constant velocity) | 1000 |
| Lewis & Miall (2003b) (Exp. B) | fMRI | 8 | 13 | Temporal discrimination (temporal vs. length) | 3000 |
| Livesey et al. (2007) | fMRI | 10 | 4 | Temporal discrimination (temporal vs. color) | 1000–1500 |
| Lux et al. (2003) | fMRI | 14 | 5 | Temporal estimation (temporal synchrony vs. spatial orientation) | 1050 |
| Morillon et al. (2009) | fMRI | 27 | 17 | Temporal estimation (duration vs. color) | 100–8400 |
| Pfeuty et al. (2015) | fMRI | 29 | 6 | Temporal estimation (duration vs. color) | 1500 |
| Pouthas et al. (2005) | fMRI | 6 | 6 | Temporal estimation (long vs. short duration) | 1300 |
| Rao et al. (2001) (Exp. A) | fMRI | 17 | 1 | Temporal discrimination (temporal perception vs. control) | 2500 |
| Rao et al. (2001) (Exp. B) | fMRI | 17 | 3 | Temporal discrimination (temporal perception vs. control) | 5000 |
| Rao et al. (2001) (Exp. C) | fMRI | 17 | 10 | Temporal discrimination (temporal perception vs. control) | 75000 |
| Rao et al. (2001) (Exp. D) | fMRI | 17 | 9 | Temporal discrimination (temporal perception vs. control) | 10000 |
| Smith et al. (2003) | fMRI | 20 | 7 | Temporal discrimination (temporal vs. order) | 1000 |
| Smith et al. (2011) | fMRI | 32 | 3 | Temporal discrimination (temporal vs. order) | 2100 |
| Tsukamoto et al. (2006) | fMRI | 20 | 13 | Temporal estimation (true vs. false feedback condition) | 3000 |
| Ustun et al. (2017) | fMRI | 15 | 10 | Temporal discrimination (time vs. visual) | 2400–6000 |
| Wiener et al. (2014) | fMRI | 25 | 17 | Temporal discrimination (time vs. color) | 2000 |

Suprasecond perceptual (nonmotor) timing condition: 22 articles, 26 experiments, 445 participants, and 250 activation foci

Figure 1. PRISMA flow chart. Overview of the selection strategy.



So, although interesting meta-analyses have been published in the last 15 years, substantial disagreement about the dynamics of functional activations of the brain structures associated with time processing still persists. Furthermore, some methodological innovations support the choice to carry out a novel meta-analysis on time perception, as the last works on this topic used an old version of GingerALE software (Ortuño et al., 2011; Wiener et al., 2010). In fact, after 2016 the BrainMap team reported some technical errors affecting this tool. In particular, codes for the thresholding procedure with both false discovery rate and cluster-level family-wise error methods were not working as expected, so that the results could be biased by false positives (for a detailed discussion, see Eickhoff, Laird, Fox, Lancaster, & Fox, 2017). In particular, Eickhoff et al. (2016) have explicitly discouraged the use of false discovery rate, in virtue of a high susceptibility to false positive results. These authors have recommended the implementation of cluster-level family-wise error thresholding, which was used in the present work, along with the new GingerALE version in which the errors of the algorithm have been corrected. Furthermore, previous meta-analyses have worked on a number of studies that were far smaller than ours. Wiener et al. (2010) examined 41 neuroimaging studies, Schwartze et al. (2012) examined 42 fMRI studies, and Ortuño et al. (2011) examined

35 studies; in contrast, this meta-analysis examined 84 studies, thus basically doubling the samples of the past.

METHODS

Selection of Studies

The MEDLINE database was queried to identify all published experiments on time perception or processing that utilized functional neuroimaging tool (fMRI or PET). Using the search engine PubMed (<https://www.ncbi.nlm.nih.gov/pubmed/>), we adopted a MeSH hierarchy routine. Furthermore, we used the function [ALL] of PubMed to find MeSH terms in all the fields of the eligible articles. The search algorithm was constructed as follows:

(time perception OR [ALL] time estimation OR [ALL] time processing [ALL]) AND (functional magnetic resonance OR [ALL] fMRI OR [ALL] positron emission tomography OR [ALL] PET [ALL]).

Additionally, references from previous review articles (Teki, 2016; Merchant, Harrington, & Meck, 2013) and meta-analyses (Schwartz et al., 2012; Ortuño et al., 2011; Wiener et al., 2010) about time perception were reviewed for inclusion. At the time of the selection phase (June 2018), over 170

full-text articles were assessed for eligibility. In particular, two expert researchers included in the meta-analysis the studies on the basis of the following criteria:

- a) articles were published in a peer-reviewed journal;
- b) articles included only healthy participants;
- c) articles adopted a whole-brain analysis (not just ROIs);
- d) articles reported coordinates of activation in Talairach/Tourneaux or in Montreal Neurological Institute stereotactic brain space;
- e) articles included at least one contrast of timing task (not contrast task-rest).

We therefore included in our meta-analysis 84 published articles, for a total of 109 experiments, 1018 coordinates of activation, and 1218 healthy participants (see Table 1 for detailed information about the sample). To facilitate the subsequent analysis, we converted all native Montreal Neurological Institute coordinates into Talairach/Tourneaux brain space using the *icbm2tal* transformation (Laird et al., 2010).

Following the previous studies of Lewis and Miall (2003a) and Wiener et al. (2010), our data set was partitioned into two main dimensions: interval duration (i.e., subsecond and suprasecond) and type (i.e., motor and nonmotor) of experimental time estimation task. Accordingly, we carried

out our meta-analysis on four distinct samples: subsecond motor (287 coordinates and 24 experiments), subsecond nonmotor (220 coordinates and 25 experiments), suprasecond motor (261 coordinates and 34 experiments), and suprasecond nonmotor (250 coordinates and 26 experiments; see also Table 1). In this data set, we included all the 41 studies considered by Wiener et al. (2010) and 21 studies—also included by Wiener et al. (2010)—of those considered by Lewis and Miall (2003a). Seven studies were excluded because one was an EEG study, one was a PET study on rhesus monkeys, four had rest contrast, and one had no dissociation between sub- and suprasecond tasks. The entire process of data selection was performed using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement international guidelines (Liberati et al., 2009; Moher, vLiberati, Tetzlaff, & Altman, 2009; for the overview of the selection strategy, see Figure 1).

Activation Likelihood Estimation and Modeled Alteration Creation

To statistically summarize the results of the retrieved experiments for each of the four conditions previously identified, we performed an activation likelihood estimation

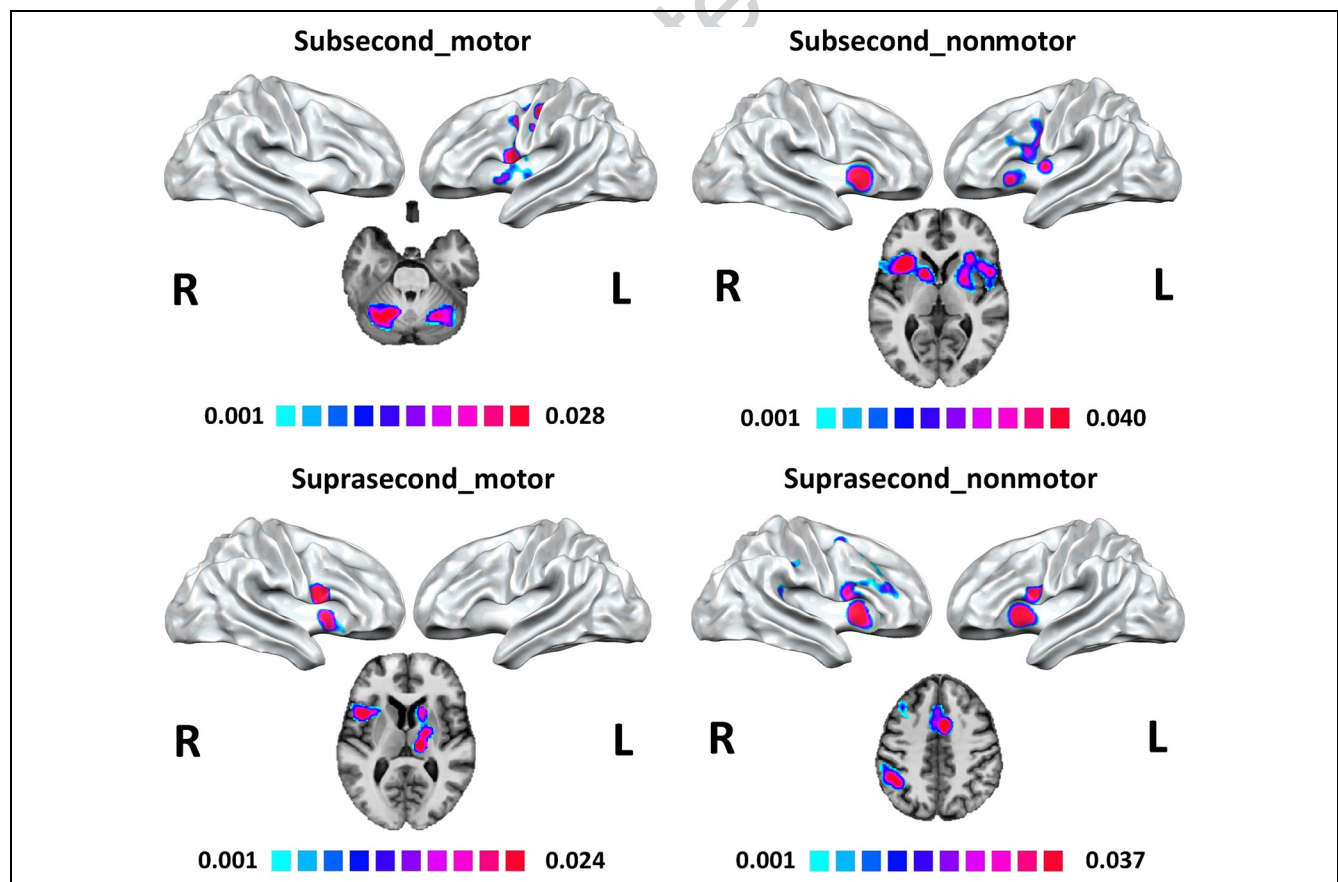


Figure 2. Results of the ALE analyses for the four conditions (cluster level corrected, $p < .05$). Colors from light blue to red represent increasing ALE values. Slices on the axial plane are shown in radiological convention (i.e., right is left, left is right).

Table 2. Significant ALE Results for the Subsecond Motor Condition Meta-analysis

| Cluster | Volume (mm ³) | Label | Side | Extrema Value | Talairach | | |
|--|---------------------------|---|------|---------------|-----------|-----|----|
| | | | | | x | y | z |
| 1 | 34,248 | Medial frontal gyrus (BA 6) | L | 0.028 | -6 | -4 | 52 |
| | | Medial frontal gyrus (BA 6) | R | 0.024 | 4 | -4 | 60 |
| | | Medial frontal gyrus (BA 6) | R | 0.022 | 8 | 4 | 56 |
| | | Precentral gyrus (BA 6) | L | 0.022 | -56 | 0 | 20 |
| | | Precentral gyrus (BA 4) | L | 0.019 | -36 | -22 | 56 |
| | | Superior frontal gyrus (BA 6) | L | 0.018 | -2 | 6 | 48 |
| | | Subgyral (BA 6) | L | 0.016 | -24 | -4 | 52 |
| | | Middle frontal gyrus (BA 6) | L | 0.013 | -26 | -10 | 42 |
| | | Cingulate gyrus (BA 32) | R | 0.012 | 10 | 10 | 36 |
| | | Precentral gyrus (BA 6) | L | 0.012 | -44 | 0 | 48 |
| | | Insula (BA 13) | L | 0.011 | -42 | -10 | 16 |
| | | Postcentral gyrus (BA 3) | L | 0.009 | -48 | -16 | 44 |
| | | Superior temporal gyrus (BA 22) | L | 0.009 | -52 | 6 | 4 |
| | | Precentral gyrus (BA 6) | L | 0.009 | -14 | -16 | 66 |
| | | Precentral gyrus (BA 44) | L | 0.008 | -50 | 0 | 8 |
| | | Superior frontal gyrus (BA 6) | R | 0.007 | 12 | 16 | 62 |
| | | Precentral gyrus (BA 6) | L | 0.007 | -48 | -2 | 34 |
| | | Superior frontal gyrus (BA 6) | L | 0.007 | -8 | 8 | 70 |
| | | Middle frontal gyrus (BA 6) | L | 0.007 | -56 | 2 | 40 |
| | | Inferior parietal lobule (BA 40) | L | 0.007 | -40 | -36 | 44 |
| Inferior frontal gyrus (BA 45) | L | 0.006 | -52 | 18 | 6 | | |
| 2 | 12,352 | Ventral posterior medial nucleus (thalamus) | L | 0.028 | -14 | -20 | 6 |
| | | Lentiform nucleus (putamen) | L | 0.022 | -26 | -8 | 6 |
| | | Clastrum | L | 0.008 | -30 | 10 | 2 |
| | | Clastrum | L | 0.006 | -32 | -8 | -8 |
| 3 | 11,752 | Lentiform nucleus (putamen) | R | 0.018 | 20 | 4 | 12 |
| | | Lentiform nucleus (putamen) | R | 0.017 | 20 | -2 | 10 |
| | | Substantia nigra | R | 0.015 | 10 | -20 | -6 |
| | | Lentiform nucleus (putamen) | R | 0.015 | 24 | -12 | 6 |
| | | Medial dorsal nucleus (thalamus) | R | 0.014 | 10 | -18 | 6 |
| | | Caudate body | R | 0.011 | 20 | 12 | 14 |
| | | Clastrum | R | 0.008 | 26 | 14 | 16 |
| | | Insula (BA 13) | R | 0.007 | 30 | 16 | 16 |
| Ventral posterior lateral nucleus (thalamus) | R | 0.007 | 24 | -24 | 10 | | |

Table 2. (continued)

| Cluster | Volume (mm ³) | Label | Side | Extrema Value | Talairach | | |
|---------|---------------------------|----------------------|------|---------------|-----------|-----|-----|
| | | | | | x | y | z |
| 4 | 9512 | Culmen (cerebellum) | R | 0.019 | 14 | -52 | -18 |
| | | Culmen (cerebellum) | R | 0.019 | 38 | -50 | -30 |
| | | Declive (cerebellum) | R | 0.014 | 28 | -60 | -22 |
| | | Tonsil (cerebellum) | R | 0.009 | 28 | -42 | -30 |
| | | Tonsil (cerebellum) | R | 0.006 | 20 | -58 | -34 |
| | | Declive (cerebellum) | R | 0.005 | 2 | -60 | -16 |
| 5 | 9336 | Culmen (cerebellum) | L | 0.012 | -22 | -56 | -24 |
| | | Tonsil (cerebellum) | L | 0.012 | -34 | -42 | -44 |
| | | Declive (cerebellum) | L | 0.011 | -30 | -58 | -18 |
| | | Tonsil (cerebellum) | L | 0.010 | -24 | -58 | -44 |
| | | Uvula (cerebellum) | L | 0.010 | -34 | -62 | -26 |
| | | Tonsil (cerebellum) | L | 0.009 | -28 | -52 | -34 |
| | | Tonsil (cerebellum) | L | 0.007 | -38 | -58 | -44 |
| | | Declive (cerebellum) | L | 0.007 | -12 | -64 | -18 |
| | | Pyramis (cerebellum) | L | 0.007 | -44 | -64 | -32 |

Contributors to Cluster 1

| | |
|---|---|
| 11 foci from Karabanov et al. (2009) | 2 foci from Jantzen et al. (2007) |
| 10 foci from Lewis et al. (2004) | 2 foci from Jantzen et al. (2004) |
| 6 foci from Schubotz & von Cramon (2001) (Exp. A) | 2 foci from Jancke et al. (2000) |
| 5 foci from Pope et al. (2005) | 2 foci from Rao et al. (1997) (Exp. A) |
| 4 foci from Ortuño et al. (2002) | 3 foci from Rao et al. (1997) (Exp. B) |
| 3 foci from Murai & Yotsumoto (2016) (Exp. A) | 2 foci from Bueti et al. (2008) (Exp. A) |
| 3 foci from Jantzen et al. (2005) | 1 focus from Berns et al. (1997) |
| 3 foci from Pastor et al. (2004) | 1 focus from Bengtsson et al. (2005) |
| 3 foci from Oullier et al. (2005) (Exp. A) | 1 focus from Penhune et al. (1998) (Exp. B) |
| 4 foci from Oullier et al. (2005) (Exp. B) | |

Contributors to Cluster 2

| | |
|---|---|
| 4 foci from Lewis et al. (2004) | 1 focus from Jantzen et al. (2005) |
| 3 foci from Mayville et al. (2002) | 1 focus from Jantzen et al. (2004) |
| 3 foci from Karabanov et al. (2009) | 1 focus from Penhune et al. (1998) (Exp. A) |
| 2 foci from Schubotz & von Cramon (2001) (Exp. A) | 1 focus from Oullier et al. (2005) (Exp. A) |
| 2 foci from Rao et al. (1997) (Exp. A) | 1 focus from Oullier et al. (2005) (Exp. B) |
| 3 foci from Rao et al. (1997) (Exp. B) | 1 focus from Bueti et al. (2008) (Exp. A) |
| 2 foci from Pope et al. (2005) | |

Table 2. (continued)

| Cluster | Volume (mm ³) | Label | Side | Extrema Value | Talairach | | |
|----------------------------------|--|-------|------|---------------|-----------|---|---|
| | | | | | x | y | z |
| <i>Contributors to Cluster 3</i> | | | | | | | |
| | 6 foci from Mayville et al. (2002) | | | | | | 2 foci from Oullier et al. (2005) (Exp. A) |
| | 6 foci from Karabanov et al. (2009) | | | | | | 2 foci from Oullier et al. (2005) (Exp. A) |
| | 2 foci from Lewis et al. (2004) | | | | | | 2 foci from Bueti et al. (2008) (Exp. A) |
| | 2 foci from Schubotz & von Cramon (2001) (Exp. A) | | | | | | 2 foci from Jantzen et al. (2004) |
| | 2 foci from Pope et al. (2005) | | | | | | |
| <i>Contributors to Cluster 4</i> | | | | | | | |
| | 3 foci from Bengtsson et al. (2005) | | | | | | 1 focus from Rao et al. (1997) (Exp. A) |
| | 3 foci from Karabanov et al. (2009) | | | | | | 1 focus from Rao et al. (1997) (Exp. B) |
| | 2 foci from Lewis et al. (2004) | | | | | | 1 focus from Pope et al. (2005) |
| | 2 foci from Mayville et al. (2002) | | | | | | 1 focus from Oullier et al. (2005) (Exp. A) |
| | 1 focus from Jantzen et al. (2004) | | | | | | 1 focus from Ortuño et al. (2002) |
| | 1 focus from Schubotz & von Cramon (2001) (Exp. A) | | | | | | 1 focus from Bueti et al. (2008) (Exp. A) |
| <i>Contributors to Cluster 5</i> | | | | | | | |
| | 2 foci from Schubotz & von Cramon (2001) (Exp. A) | | | | | | 1 focus from Pope et al. (2005) |
| | 2 foci from Karabanov et al. (2009) | | | | | | 1 focus from Penhune et al. (1998) (Exp. A) |
| | 2 foci from Aso et al. (2010) (Exp. A) | | | | | | 1 focus from Penhune et al. (1998) (Exp. B) |
| | 1 focus from Lewis et al. (2004) | | | | | | 1 focus from Oullier et al. (2005) (Exp. A) |
| | 1 focus from Jantzen et al. (2007) | | | | | | 1 focus from Oullier et al. (2005) (Exp. B) |
| | 1 focus from Jantzen et al. (2005) | | | | | | 1 focus from Ortuño et al. (2002) |
| | 1 focus from Jantzen et al. (2004) | | | | | | 1 focus from Bueti et al. (2008) (Exp. A) |

For each cluster brain regions, cluster size (mm³), side (hemisphere), ALE value, Talairach coordinates, and contributors to cluster (foci) were provided. BA = Brodmann's area; L = left; R = right.

(ALE) as implemented in GingerAle 2.3.6 (Eickhoff, Bzdok, Laird, Kurth, & Fox, 2012; Turkeltaub et al., 2012; Eickhoff et al., 2009). The four resulting maps have been clustered at a level of $p < .05$, family-wise error-corrected for multiple comparisons, with a cluster-forming threshold of $p < .001$ (Eickhoff et al., 2016, 2017).

The ALE is a technique capable of providing information about the reliability of results by means of a comparison between the experiments and a sample of reference studies from the existing literature (Laird et al., 2005). An ALE meta-analysis considers every experiment focus as being a Gaussian probability distribution:

$$p(d) = \frac{1}{\sigma^3 \sqrt{(2\pi)^3}} e^{-\frac{d^2}{2\sigma^2}}$$

in which d is the Euclidean distance between the focus and the voxels whereas σ is the standard deviation of the distribution.

A modeled alteration map is then determined for every experiment as the combination of the Gaussian probability distribution of every experiment focus. Subsequently, the ALE map is obtained from the union of all the modeled alteration maps.

The ALE map is thresholded on the basis of a null hypothesis, obtained recursively by producing all the possible random distribution of foci. Then, to obtain a cluster-level correction, a similar procedure is repeated to define the size of nonrandom clusters of activation. The significance of values within the ALE map is finally calculated by testing the null hypothesis that active voxels are randomly distributed across the brain. The iterative

Table 3. Significant ALE Results for the Subsecond Perceptual Condition Meta-analysis

| Cluster | Volume (mm ³) | Label | Side | Extrema Value | Talairach | | |
|-----------------------------|---------------------------|-------------------------------------|------|---------------|-----------|-----|----|
| | | | | | x | y | z |
| 1 | 25,192 | Claustrum | L | 0.031 | -30 | -6 | 12 |
| | | Inferior frontal gyrus (BA 47) | L | 0.022 | -48 | 12 | 0 |
| | | Claustrum | L | 0.020 | -28 | 24 | 4 |
| | | Precentral gyrus (BA 44) | L | 0.019 | -46 | 8 | 12 |
| | | Lentiform nucleus (putamen) | L | 0.017 | -22 | 2 | 8 |
| | | Precentral gyrus (BA 6) | L | 0.016 | -46 | 0 | 32 |
| | | Middle frontal gyrus (BA 6) | L | 0.015 | -24 | -8 | 50 |
| | | Inferior frontal gyrus (BA 9) | L | 0.015 | -52 | 10 | 26 |
| | | Insula (BA 13) | L | 0.014 | -40 | 14 | 6 |
| | | Lentiform nucleus (putamen) | L | 0.014 | -24 | 10 | 4 |
| | | Precentral gyrus (BA 6) | L | 0.009 | -48 | -2 | 8 |
| | | Middle frontal gyrus (BA 6) | L | 0.009 | -38 | 2 | 46 |
| | | Middle frontal gyrus (BA 9) | L | 0.008 | -48 | 22 | 32 |
| | | Middle frontal gyrus (BA 46) | L | 0.008 | -46 | 22 | 20 |
| | | Middle frontal gyrus (BA 6) | L | 0.007 | -48 | 4 | 48 |
| Middle frontal gyrus (BA 9) | L | 0.006 | -46 | 32 | 38 | | |
| 2 | 14,896 | Insula (BA 13) | R | 0.032 | 34 | 18 | 6 |
| | | Caudate body | R | 0.022 | 14 | 8 | 6 |
| | | Insula (BA 13) | R | 0.014 | 44 | 10 | 16 |
| | | Superior temporal gyrus (BA 22) | R | 0.011 | 50 | 12 | 0 |
| | | Lentiform nucleus (globus pallidus) | R | 0.010 | 20 | -2 | -6 |
| 3 | 13,208 | Cingulate gyrus (BA 32) | L | 0.040 | 0 | 28 | 34 |
| | | Superior frontal gyrus (BA 6) | R | 0.023 | 2 | 10 | 50 |
| | | Medial frontal gyrus (BA 6) | L | 0.016 | -2 | -4 | 54 |
| | | Cingulate gyrus (BA 32) | L | 0.008 | -12 | 6 | 40 |
| | | Medial frontal gyrus (BA 6) | L | 0.008 | -4 | -18 | 52 |

Contributors to Cluster 1

6 foci from Tomasi et al. (2015)

5 foci from Schubotz & von Cramon (2001) (Exp. B)

4 foci from Lewis & Miall (2003b)

4 foci from Ferrandez et al. (2003)

3 foci from Tregellas et al. (2006)

3 foci from Schubotz et al. (2000)

2 foci from Beudel et al. (2009) (Exp. A)

2 foci from Shih et al. (2009)

2 foci from Bueti et al. (2008)

1 focus from Wittmann et al. (2010a) (Exp. A)

1 focus from Wittmann et al. (2010a) (Exp. C)

1 focus from van Wassenhove et al. (2011) (Exp. A)

1 focus from van Wassenhove et al. (2011) (Exp. B)

1 focus from Coull & Nobre (1998) (Exp. A)

Table 3. (continued)

| Cluster | Volume (mm ³) | Label | Side | Extrema Value | Talairach | | |
|--|---------------------------|-------|------|---------------|-----------|---|---|
| | | | | | x | y | z |
| 2 foci from Bengtsson et al. (2009) (Exp. A) | | | | | | | |
| 2 foci from Tipples et al. (2013) | | | | | | | |
| <i>Contributors to Cluster 2</i> | | | | | | | |
| 5 foci from Tomasi et al. (2015) | | | | | | | |
| 3 foci from Lewis & Miall (2003b) | | | | | | | |
| 3 foci from Tipples et al. (2013) | | | | | | | |
| 3 foci from Schubotz & von Cramon (2001) (Exp. B) | | | | | | | |
| 2 foci from Tregellas et al. (2006) | | | | | | | |
| 2 foci from Schubotz et al. (2000) | | | | | | | |
| 1 focus from Wittmann et al. (2010a) (Exp. B) | | | | | | | |
| 1 focus from van Wassenhove et al. (2011) (Exp. B) | | | | | | | |
| <i>Contributors to Cluster 3</i> | | | | | | | |
| 3 foci from Bengtsson et al. (2009) (Exp. A) | | | | | | | |
| 2 foci from Lewis & Miall, 2003b | | | | | | | |
| 2 foci from Ferrandez et al. (2003) | | | | | | | |
| 2 foci from Tipples et al. (2013) | | | | | | | |
| 2 foci from Shih et al. (2009) | | | | | | | |
| 2 foci from Schubotz & von Cramon (2001) (Exp. B) | | | | | | | |
| 1 focus from Wittmann et al. (2010a) (Exp. A) | | | | | | | |
| 1 focus from Wittmann et al. (2010a) (Exp. B) | | | | | | | |
| 1 focus from van Wassenhove et al. (2011) (Exp. A) | | | | | | | |

For each cluster brain regions, cluster size (mm³), side (hemisphere), ALE value, Talairach coordinates, and contributors to cluster (foci) were provided. BA = Brodmann's area; L = left; R = right.

process generates a vector that can be considered as a histogram representing the null distribution. Voxel-level thresholds can be obtained from this. The cluster-level threshold is obtained through the calculation of the cluster size distribution, after 1000 permutations (Acar, Seurinck, Eickhoff, & Moerkerke, 2018).

Correlation between Maps and Voxels' Contribution to Correlation Analysis

To compare the four different conditions, we computed all the possible correlations between the maps. To do so, we computed the linear correlation, by means of Pearson's r , between the two matrices containing the voxel values of the map associated with each condition.

For every condition, we further analyzed the voxel-wise contribution to the correlation. This is an innovative mapping analysis that allows us to appreciate the marginal contribution of each voxel in the correlation of two maps, so as to better identify the voxels exerting more influence in the correlation. Specifically, to examine the regional differences between the four conditions, we applied the analysis leave-one-voxel-out so as to evaluate the voxels' contribution to the correlation (VCC) between the maps (Mancuso et al., 2019). Every pair of corresponding voxels v_{i1} and v_{i2} was removed from both maps, and after every removal, the Pearson's r between the two maps was recalculated. The difference $r_{\text{GLOBAL}} - R_{\text{VIREMOVED}}$ between the original value of r and the value obtained after removing the couple of voxels v_{i1} and v_{i2} was attributed to voxel v_i . This procedure was repeated for v_j, v_k, \dots ; then,

Table 4. Significant ALE Results for the Suprasecond Motor Condition Meta-analysis

| Cluster | Volume(mm ³) | Label | Side | Extrema Value | Talairach | | |
|---------|--------------------------|--------------------------------------|------|---------------|-----------|-----|----|
| | | | | | x | Y | Z |
| 1 | 19,008 | Superior frontal gyrus (BA 6) | L | 0.024 | -2 | 10 | 50 |
| | | Medial frontal gyrus (BA 6) | R | 0.020 | 2 | 0 | 62 |
| | | Cingulate gyrus (BA 32) | R | 0.018 | 6 | 20 | 36 |
| | | Medial frontal gyrus (BA 6) | L | 0.011 | -10 | -22 | 46 |
| | | Cingulate gyrus (BA 32) | L | 0.009 | -6 | 24 | 34 |
| | | Medial frontal gyrus (BA 8) | L | 0.009 | -4 | 28 | 42 |
| | | Paracentral lobule (BA 31) | L | 0.007 | -2 | -24 | 42 |
| 2 | 11,784 | Inferior frontal gyrus (BA 44) | R | 0.023 | 52 | 8 | 22 |
| | | Insula (BA 13) | R | 0.020 | 42 | 12 | 6 |
| | | Inferior frontal gyrus (BA 47) | R | 0.014 | 36 | 20 | -4 |
| | | Clastrum | R | 0.010 | 30 | 14 | 6 |
| | | Inferior frontal gyrus (BA 45) | R | 0.009 | 46 | 28 | 4 |
| | | Superior temporal gyrus (BA 22) | R | 0.005 | 56 | 8 | 4 |
| 3 | 6824 | Mammillary body | L | 0.020 | -12 | -18 | 4 |
| | | Lentiform nucleus (putamen) | L | 0.013 | -18 | -6 | 12 |
| | | Caudate body | L | 0.010 | -14 | 8 | 12 |
| | | Lateral posterior nucleus (thalamus) | L | 0.008 | -14 | -18 | 18 |

Contributors to Cluster 1

| | |
|--|---|
| 3 foci from Dudukovic & Wagner (2007) | 1 focus from Wittmann et al. (2010b) (Exp. B) |
| 3 foci from Stevens et al. (2007) | 1 focus from Wittmann et al. (2010b) (Exp. C) |
| 2 foci from Lewis & Miall (2002) | 1 focus from Murai & Yotsumoto (2016) |
| 2 foci from Larsson et al. (1996) | 1 focus from Lejeune et al. (1997) |
| 2 foci from Taniwaki et al. (2006) | 1 focus from Jech et al. (2005) |
| 2 foci from Rubia et al. (1998) | 1 focus from Coull et al. (2013) (Exp. A) |
| 2 foci from Riecker et al. (2003) | 1 focus from Basso et al. (2003) |
| 2 foci from Macar et al. (2002) | 1 focus from Shergill et al. (2006) |
| 1 focus from Wittmann et al. (2011) (Exp. A) | 1 focus from Riecker et al. (2006) |
| 1 focus from Wittmann et al. (2011) (Exp. B) | 1 focus from Rekkas et al. (2005) (Exp. B) |
| 1 focus from Wittmann et al. (2011) (Exp. C) | 1 focus from Macar et al. (2004) |

Contributors to Cluster 2

| | |
|---|---|
| 2 foci from Wittmann et al. (2010) (Exp. B) | 1 focus from Wittmann et al. (2010b) (Exp. C) |
| 2 foci from Coull et al. (2013) (Exp. A) | 1 focus from Murai & Yotsumoto (2016) |
| 2 foci from Ackermann et al. (2001) | 1 focus from Lewis & Miall (2002) |
| 2 foci from Shergill et al. (2006) | 1 focus from Lejeune et al. (1997) |

Table 4. (continued)

| Cluster | Volume(mm ³) | Label | Side | Extrema Value | Talairach | | |
|---|--------------------------|-------|---|---------------|-----------|---|---|
| | | | | | x | Y | Z |
| 1 focus from Wittmann et al. (2011) (Exp. A) | | | 1 focus from Brunia et al. (2000) | | | | |
| 1 focus from Wittmann et al. (2011) (Exp. B) | | | 1 focus from Basso et al. (2003) | | | | |
| 1 focus from Wittmann et al. (2011) (Exp. C) | | | 1 focus from Taniwaki et al. (2006) | | | | |
| 1 focus from Wittmann et al. (2010b) (Exp. A) | | | 1 focus from Stevens et al. (2007) | | | | |
| <i>Contributors to Cluster 3</i> | | | | | | | |
| 3 foci from Riecker et al. (2006) | | | 1 focus from Coull et al. (2013) (Exp. A) | | | | |
| 2 foci from Taniwaki et al. (2006) | | | 1 focus from Ackermann et al. (2001) | | | | |
| 2 foci from Riecker et al. (2003) | | | 1 focus from Stevens et al. (2007) | | | | |
| 1 focus from Teki et al. (2016) | | | 1 focus from Shergill et al. (2006) | | | | |

For each cluster brain regions, cluster size (mm³), side (hemisphere), ALE value, Talairach coordinates, and contributors to cluster (foci) were provided. BA = Brodmann's area; L = left; R = right.

the difference values were normalized, so as to obtain a voxel-wise estimation of the local contribution to the global correlation.

Negative VCC values denote the voxels whose removal produces an increase of the correlation, which means that they do not positively contribute to the global r . In contrast, positive VCC values denote the voxels contributing to a positive correlation between the two maps, whose removal determines an r_{GLOBAL} decrease. The VCC can therefore provide us with the information about the regions that contribute to the similarity and the dissimilarity of the two maps.

Hierarchical Clustering and Features of Relevance Estimation

To better investigate the differences and commonalities between the various conditions, we applied a hierarchical clustering analysis using as entry elements the four obtained ALE maps. As a first step, the peak ALE values for each of the ROIs were calculated. Parcels were identified on the basis of the Talairach Atlas. The 113 ROIs that showed nonzero peak values at least in one of the four conditions were passed to subsequent analyses, performed using the Orange Canvas software. An $N \times M$ matrix (4 conditions \times 113 ROIs) was used as input. Euclidean distances were computed between rows (i.e., between conditions), and hierarchical clustering was performed with the Ward's linkage method. We then used the information gain (IG) criterion (Alhaj, Siraj, Zainal, Elshoush, & Elhaj, 2016) to identify the most informative brain regions capable of distinguishing between the four conditions. The IG is based on a

measure of entropy and is commonly used in the feature-ranking procedures, so as to identify those features that are particularly relevant for the accurate implementation of a given task (e.g., to assign an item to the correct class among many).

Reliability Analysis

To investigate the reliability of the obtained results, we applied the "fail-safe" technique. This kind of approach, frequently used in classical meta-analyses, was first introduced by Rosenthal (1979), and recently, Acar et al. (2018) made it suitable for ALE meta-analyses. This method addresses the issue of the so-called "file-drawer effect," that is, the smaller chance for a study to show nonstatistically significant results to get published. This bias could lead to overestimated effects in meta-analyses because of the lack of contraevidences in the pool of considered studies. The procedure that we used, proposed by Acar, Seurinck, Eickhoff, and Moerkerke (2017; <https://github.com/NeuroStat/GenerateNull>), allows to introduce "noise experiments" to the meta-analysis pool. The injection of growing levels of noise raises the statistical threshold, allowing to test how many unpublished experiments should exist to nullify the obtained results. More in details, the Acar's algorithm observes the distributions of sample size and amount of reported foci per experiment in the pool of real experiments. These two parameters are pivotal for the implementation of the ALE method and the identification of the effect (Eickhoff et al., 2016). Noise experiments are then created randomly by combining values of sample size and amount of reported foci per experiment taken from the respective real distributions (Acar et al., 2017). The

Table 5. Significant ALE Results for the Suprasecond Perceptual Condition Meta-analysis

| Cluster | Volume (mm ³) | Label | Side | Extrema Value | Talairach | | |
|---------|---------------------------|----------------------------------|------|---------------|-----------|-----|----|
| | | | | | x | y | z |
| 1 | 19,240 | Insula (BA 13) | R | 0.037 | 34 | 16 | 6 |
| | | Inferior frontal gyrus (BA 44) | R | 0.025 | 50 | 10 | 20 |
| | | Middle frontal gyrus (BA 9) | R | 0.016 | 36 | 32 | 32 |
| | | Middle frontal gyrus (BA 10) | R | 0.011 | 32 | 44 | 2 |
| | | Middle frontal gyrus (BA 46) | R | 0.010 | 44 | 40 | 26 |
| | | Middle frontal gyrus (BA 6) | R | 0.009 | 30 | 16 | 50 |
| | | Inferior frontal gyrus (BA 46) | R | 0.008 | 44 | 32 | 6 |
| | | Middle frontal gyrus (BA 9) | R | 0.008 | 44 | 22 | 28 |
| | | Precentral gyrus (BA 6) | R | 0.008 | 38 | 2 | 32 |
| | | Inferior frontal gyrus (BA 45) | R | 0.007 | 60 | 24 | 12 |
| 2 | 16,848 | Medial frontal gyrus (BA 32) | L | 0.030 | -4 | 8 | 46 |
| | | Medial frontal gyrus (BA 6) | L | 0.030 | -6 | 4 | 52 |
| | | Superior frontal gyrus (BA 6) | R | 0.024 | 6 | 10 | 54 |
| | | Cingulate gyrus (BA 32) | R | 0.013 | 12 | 28 | 26 |
| | | Medial frontal gyrus (BA 8) | R | 0.012 | 2 | 22 | 46 |
| | | Middle frontal gyrus (BA 6) | R | 0.012 | 30 | 4 | 62 |
| | | Medial frontal gyrus (BA 9) | R | 0.011 | 2 | 34 | 30 |
| | | Superior frontal gyrus (BA 9) | R | 0.011 | 22 | 40 | 30 |
| | | Superior frontal gyrus (BA 6) | R | 0.010 | 22 | 6 | 60 |
| | | Superior frontal gyrus (BA 6) | R | 0.009 | 16 | 16 | 54 |
| | | Middle frontal gyrus (BA 6) | R | 0.008 | 30 | 2 | 52 |
| 3 | 16,016 | Clastrum | L | 0.033 | -34 | 14 | 4 |
| | | Inferior frontal gyrus (BA 44) | L | 0.028 | -48 | 6 | 20 |
| | | Lentiform nucleus (putamen) | L | 0.014 | -14 | 8 | -4 |
| | | Lentiform nucleus (putamen) | L | 0.011 | -16 | 4 | 4 |
| | | Middle frontal gyrus (BA 9) | L | 0.009 | -54 | 8 | 36 |
| | | Middle frontal gyrus (BA 9) | L | 0.008 | -40 | 14 | 28 |
| | | Precentral gyrus (BA 44) | L | 0.006 | -50 | 12 | 4 |
| 4 | 7368 | Inferior parietal lobule (BA 40) | R | 0.020 | 48 | -42 | 42 |
| | | Inferior parietal lobule (BA 40) | R | 0.019 | 40 | -48 | 42 |
| | | Insula (BA 13) | R | 0.009 | 52 | -34 | 20 |
| | | Superior temporal gyrus (BA 13) | R | 0.009 | 52 | -42 | 22 |
| | | Inferior parietal lobule (BA 40) | R | 0.009 | 54 | -32 | 46 |
| | | Superior temporal gyrus (BA 41) | R | 0.009 | 54 | -28 | 10 |
| | | Superior temporal gyrus (BA 22) | R | 0.005 | 54 | -38 | 10 |

Table 5. (continued)

| Cluster | Volume (mm ³) | Label | Side | Extrema Value | Talairach | | |
|----------------------------------|---|-------|------|---------------|-----------|---|---|
| | | | | | x | y | z |
| <i>Contributors to Cluster 1</i> | | | | | | | |
| | 6 foci from Lewis & Miall (2003b) | | | | | | |
| | 4 foci from Carvalho et al. (2016) (Exp. A) | | | | | | |
| | 4 foci from Smith et al. (2003) | | | | | | |
| | 3 foci from Pfeuty et al. (2015) | | | | | | |
| | 3 foci from Morillon et al. (2009) | | | | | | |
| | 3 foci from Coull et al. (2013) (Exp. B) | | | | | | |
| | 2 foci from Ustun et al. (2017) | | | | | | |
| | 2 foci from Jueptner et al. (1996) | | | | | | |
| | 2 foci from Coull et al. (2000) | | | | | | |
| <i>Contributors to Cluster 2</i> | | | | | | | |
| | 3 foci from Coull et al. (2004) | | | | | | |
| | 3 foci from Carvalho et al. (2016)(Exp. A) | | | | | | |
| | 2 foci from Wiener et al. (2014) | | | | | | |
| | 2 foci from Morillon et al. (2009) | | | | | | |
| | 2 foci from Harrington et al. (2004) | | | | | | |
| | 2 foci from Coull et al. (2000) | | | | | | |
| | 2 foci from Smith et al. (2003) | | | | | | |
| | 2 foci from Pouthas et al. (2005) | | | | | | |
| | 1 focus from Ustun et al. (2017) | | | | | | |
| | 1 focus from Smith et al. (2011) | | | | | | |
| <i>Contributors to Cluster 3</i> | | | | | | | |
| | 3 foci from Lewis & Miall (2003b) | | | | | | |
| | 3 foci from Harrington et al. (2010) | | | | | | |
| | 3 foci from Carvalho et al. (2016) (Exp. A) | | | | | | |
| | 3 foci from Rao et al. (2001) (Exp. D) | | | | | | |
| | 2 foci from Ustun et al. (2017) | | | | | | |
| | 2 foci from Livesey et al. (2007) | | | | | | |
| | 2 foci from Coull et al. (2013) (Exp. B) | | | | | | |
| | 2 foci from Coull et al. (2000) | | | | | | |
| <i>Contributors to Cluster 4</i> | | | | | | | |
| | 2 foci from Harrington et al. (2004) | | | | | | |
| | 2 foci from Carvalho et al. (2016) (Exp. B) | | | | | | |
| | 2 foci from Tsukamoto et al. (2006) | | | | | | |

Table 5. (continued)

| Cluster | Volume (mm ³) | Label | Side | Extrema Value | Talairach | | |
|-------------------------------------|---------------------------|-------|------|---------------|-----------|---|---|
| | | | | | x | y | z |
| 1 focus from Ustun et al. (2017) | | | | | | | |
| 1 focus from Smith et al. (2011) | | | | | | | |
| 1 focus from Morillon et al. (2009) | | | | | | | |

For each cluster brain regions, cluster size (mm³), side (hemisphere), ALE value, Talairach coordinates, and contributors to cluster (foci) were provided. BA = Brodmann's area; L = left; R = right.

final step is the repetition of the ALE analysis using as input the real pool injected with variable amount of noise experiments.

In this study, the range of injected noise was between $\frac{k}{4}$ and $3k$, where k is the number of real experiments. In each repetition, we added the $\frac{k}{4}$ of noise (i.e., 12 ALE maps). Finally, we created a map showing the residual real contribution of each brain area after an increasing injection of noise. Because the sample size and the amount of reported foci per experiment are specific for each pool used for a meta-analysis, we repeated the fail-safe procedure for each of the four conditions investigated in this study.

RESULTS

The Patterns of Brain Areas Involved in Time Perception

The ALE analysis of the subsecond motor condition shows activations mainly localized in medial and superior frontal gyri, left precentral gyrus, right cingulate gyrus, left superior temporal gyrus, left inferior parietal lobule, insula, right claustrum, thalamus, putamen, right caudate body, substantia nigra, and cerebellum (Figure 2 and Table 2).

The ALE analysis of the subsecond perceptual condition shows activations mainly localized in the left claustrum, left middle, medial and inferior frontal gyri, left precentral gyrus, left putamen, insula, right caudate body, right superior temporal gyrus, right globus pallidus, left cingulate gyrus, and right superior frontal gyrus (Figure 2 and Table 3).

The ALE analysis of the suprasecond motor condition shows activations mainly localized in left superior frontal gyrus, medial frontal gyrus, cingulate gyrus, right inferior frontal gyrus, right insula, right claustrum, right superior temporal gyrus, left mammillary body, left putamen, left caudate body, and left thalamus (Figure 2 and Table 4).

The ALE analysis of the suprasecond perceptual condition shows activations mainly localized in right insula, right middle and inferior frontal gyri, precentral gyrus, left medial frontal gyrus, right superior frontal gyrus, right cingulate gyrus, right medial frontal gyrus, left claustrum, left inferior frontal gyrus, left putamen, left middle frontal gyrus, right inferior parietal lobule, and right superior temporal gyrus (Figure 2 and Table 5).

Correlation between Maps and Voxels' Contribution to Correlation Analysis

With regard to the correlation analyses, the highest value ($r = .51$) was found between subperceptual and suprapreperceptual conditions (Table 6). The correlation between supramotor versus suprapreperceptual was $r = .38$, followed by submotor versus supramotor ($r = .36$) and submotor versus subperceptual ($r = .23$). In light of this, the submotor condition is more correlated with the supramotor than the subperceptual. The subperceptual condition is more correlated with the suprapreperceptual than the submotor. The supramotor condition is more correlated with the suprapreperceptual than the submotor. Finally, the suprapreperceptual condition is more correlated with the subperceptual than the supramotor.

Table 6. Correlation Values (Pearson's r) between Each Couple of Conditions

| | Subsecond motor | Subsecond perceptual | Suprasecond motor | Suprasecond perceptual |
|------------------------|-----------------|----------------------|-------------------|------------------------|
| Subsecond motor | | 0.23 | 0.36 | 0.18 |
| Subsecond perceptual | | | 0.37 | 0.51 |
| Suprasecond motor | | | | 0.38 |
| Suprasecond perceptual | | | | |

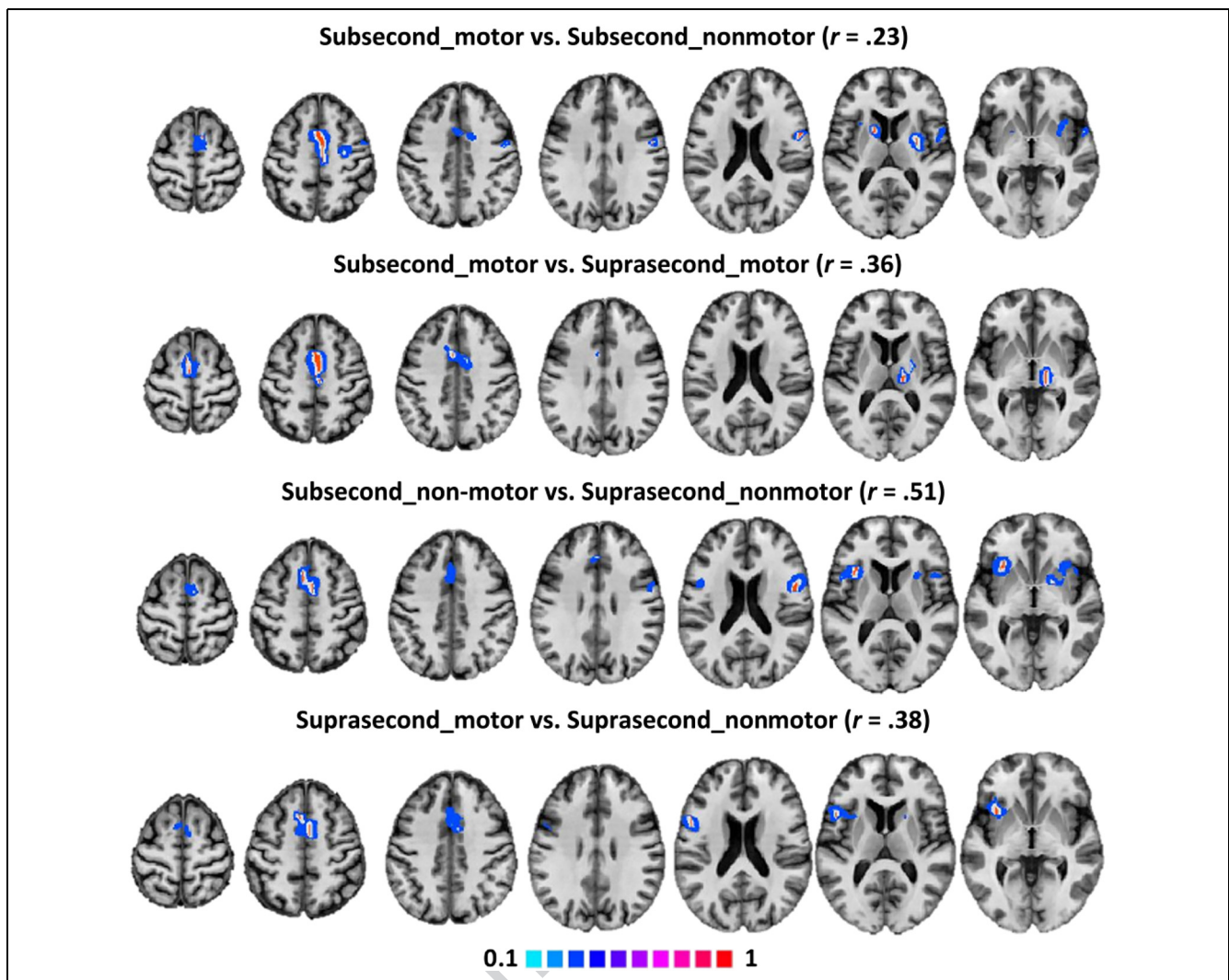


Figure 3. Results of the contribution leave-one-voxel-out to the correlation analyses. Colors from light blue to red represent increasing contribution to the overall correlation between the two conditions (values were normalized between 0 and 1). Values of r are the results of the correlation before the leave-one-out procedure. Slices on the axial plane are shown in radiological convention (i.e., right is left, left is right).

The VCC analysis produced the following results. The voxels driving the correlation between the subsecond motor and subsecond perceptual conditions are mainly localized in the left superior and middle frontal gyrus, left superior insula, right caudate body, left precentral gyrus, and right lateral globus pallidus (Figure 3).

The voxels driving the correlation between the subsecond motor and suprasecond motor conditions are mainly localized in the bilateral medial frontal gyrus, the left ventral posterior lateral nucleus of the thalamus, and the left putamen (Figure 3).

The voxels driving the correlation between the subsecond perceptual and the suprasecond perceptual conditions are mainly localized in the right superior and medial frontal gyrus, bilateral anterior insula, left inferior frontal gyrus, and left putamen (Figure 3).

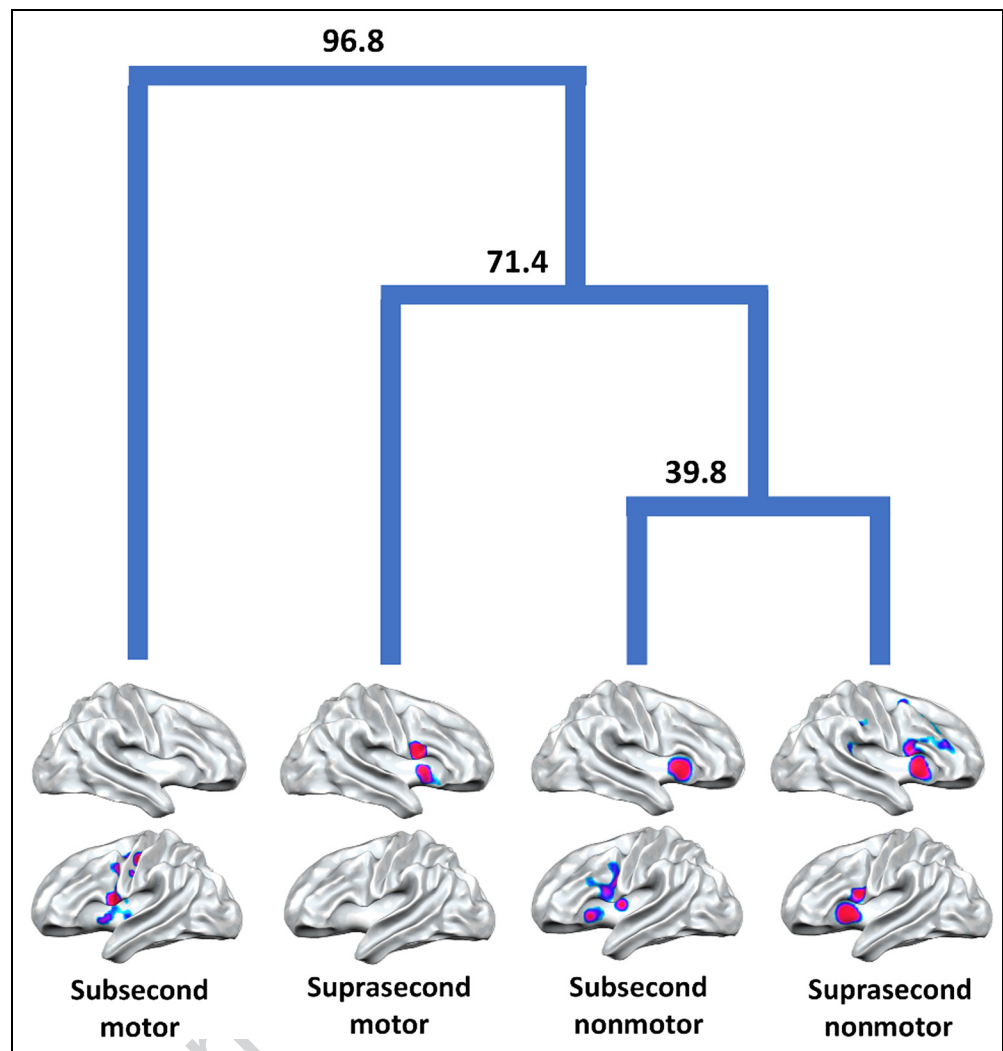
The voxels driving the correlation between the suprasecond motor and the suprasecond perceptual conditions

are mainly localized in the right superior, medial and inferior frontal gyri, and left putamen (Figure 3).

Hierarchical Clustering and Features of Relevance Estimation

The dendrogram obtained through the hierarchical clustering shows the highest similarity between the two perceptual conditions (i.e., sub- and suprasecond). The suprasecond motor condition results to be more similar to the perceptual cluster than to the subsecond motor condition (Figure 4). This configuration is coherent with the correlation results, because the highest value was found between the two perceptual conditions. The suprasecond motor condition shows a slightly higher correlation with the suprasecond perceptual condition rather than with the subsecond motor one. The IG identifies the left BA 31, left and right putamen, right BA 6, right

Figure 4. Results of the hierarchical clustering. Dendrogram was built using the Ward's linkage. The nodes' values represent dissimilarity.



BA 32, left BA 45, left BA 8, right ventral anterior nucleus of the thalamus, left lateral and medial globus pallidus, right BA 44, left posterior and anterior BA 13, left BA 22, left BA 47, left caudate body, left BA 43, left BA 4, and right BA 24 as the most informative areas for discriminating between conditions. Of note, none of these brain regions was active in only one of the four conditions.

The overlap of the patterns of activations obtained with the ALE maps associated with the four conditions identifies the SMA as the area in which conditions show the greatest overlap (100%; Figure 5).

As the SMA appears to be the area with the greatest overlap between conditions, we have examined how its activation can vary in relation to sub- and suprasecond tasks, as well as to motor and nonmotor tasks (Figure 6).

Reliability

The fail-safe analysis shows a good resistance of the results (Figure 7). Most of the activation blobs, across the four conditions, survive after the 50% level of noise is injected. Of note, the SMA is still present even after the

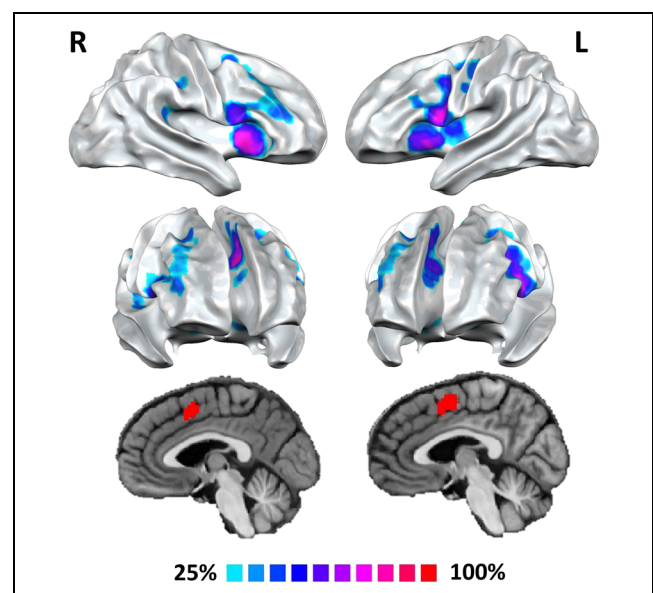
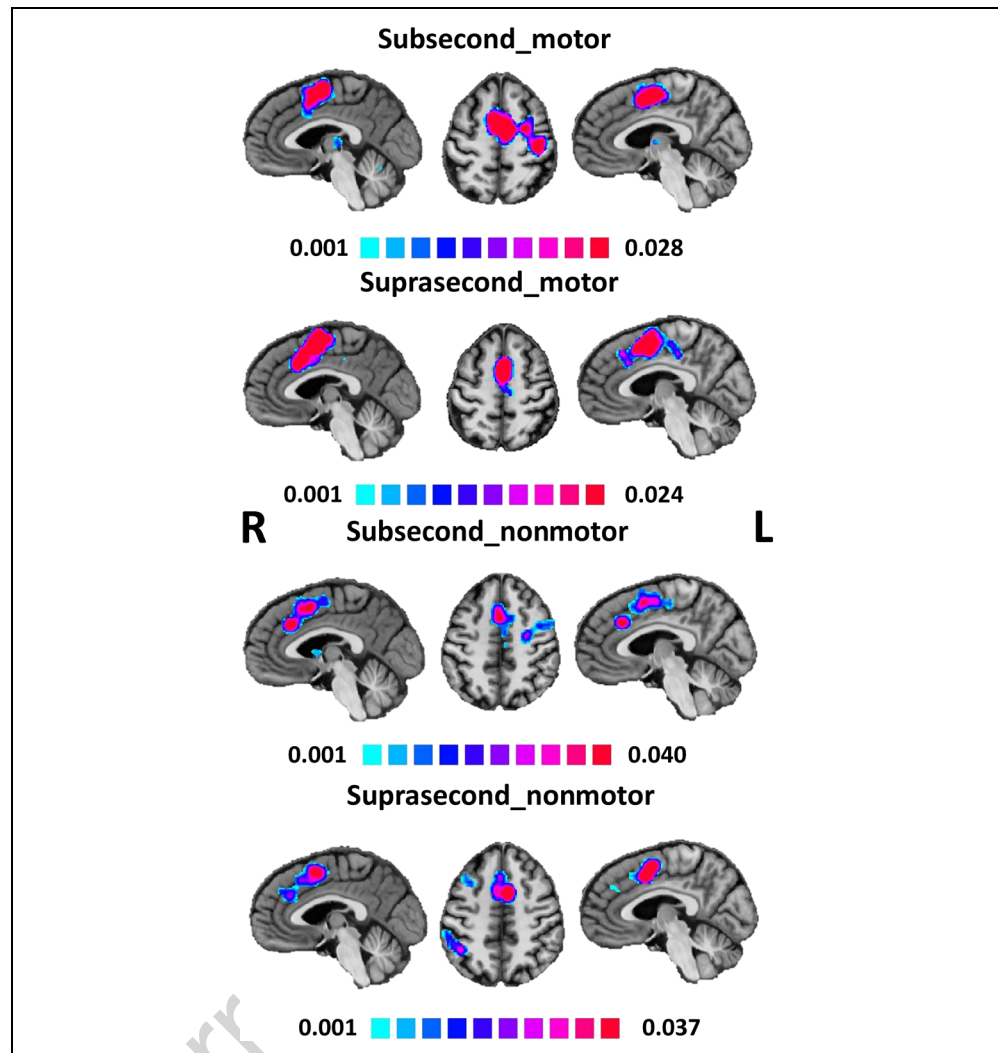


Figure 5. Overlap between the ALE maps associated to each of the four conditions. Colors from light blue to red represent increasing overlap values. Voxels showing value equal to 100% were found to be active through all the four conditions. Slices on the axial plane are shown in radiological convention (i.e., right is left, left is right).

Figure 6. Sagittal and axial sections of the ALE in all the four conditions in which the different activation profile of the SMA can be appreciated. Colors from light blue to red represent increasing ALE values. Slices on the axial plane are shown in radiological convention (i.e., right is left, left is right).



injection of the 300% of noise in three of the four conditions (the exception is the subsecond perceptual). Subcortical regions show a good resistance, especially with regard to the subsecond conditions (motor and nonmotor), where they survive above the 50% of the noise level. A similar trend is observed for the insula as well.

Overall, the fail-safe analysis about the robustness of our results is reassuring, as most of them have maintained significance after noise injections of 50% and the SMA even after an injection of 300% of noise.

DISCUSSION

Our meta-analytical investigation, which used a new corrected version for the ALE and an innovative fail-safe technique, mostly confirms the findings of the previous meta-analyses. However, patterns of activation related to subsecond and suprasecond tasks are much more similar than previously thought. Both subsecond and suprasecond tasks recruit cortical and subcortical areas, but

subcortical areas contribute more to the pattern associated with subsecond tasks than to the pattern associated with suprasecond tasks, which instead receives more contributions from cortical activations. This is in line with the idea that distinct timing mechanisms may operate at different timescales (Buhusi & Meck, 2005), as well as to the idea that intervals below the 1-sec range are supposed to be more dependent on sensory and automatic processes, whereas the detection and estimation of intervals longer than 1 sec are thought to rely more on cognitive functions (Lewis & Miall, 2003a; Rammsayer, 1999). Several cognitive processes are in fact likely to contribute to the perception/construction of time (Meck, 2005; Pouthas & Perbal, 2004). For instance, the degree of attention can modulate and influence the estimate of time (Coull, Vidal, Nazarian, & Macar, 2004; Nobre & O'Reilly, 2004). Also, working memory and executive processes come into play in time judgments (Radua, Del Pozo, Gomez, Guillen-Grima, & Ortuño, 2014). In tasks when the participant is required to compare the different durations of two stimuli, the duration of the first stimulus must be held in the STM storage so as to decide which stimulus is longer (Livesey, Wall, & Smith, 2007).

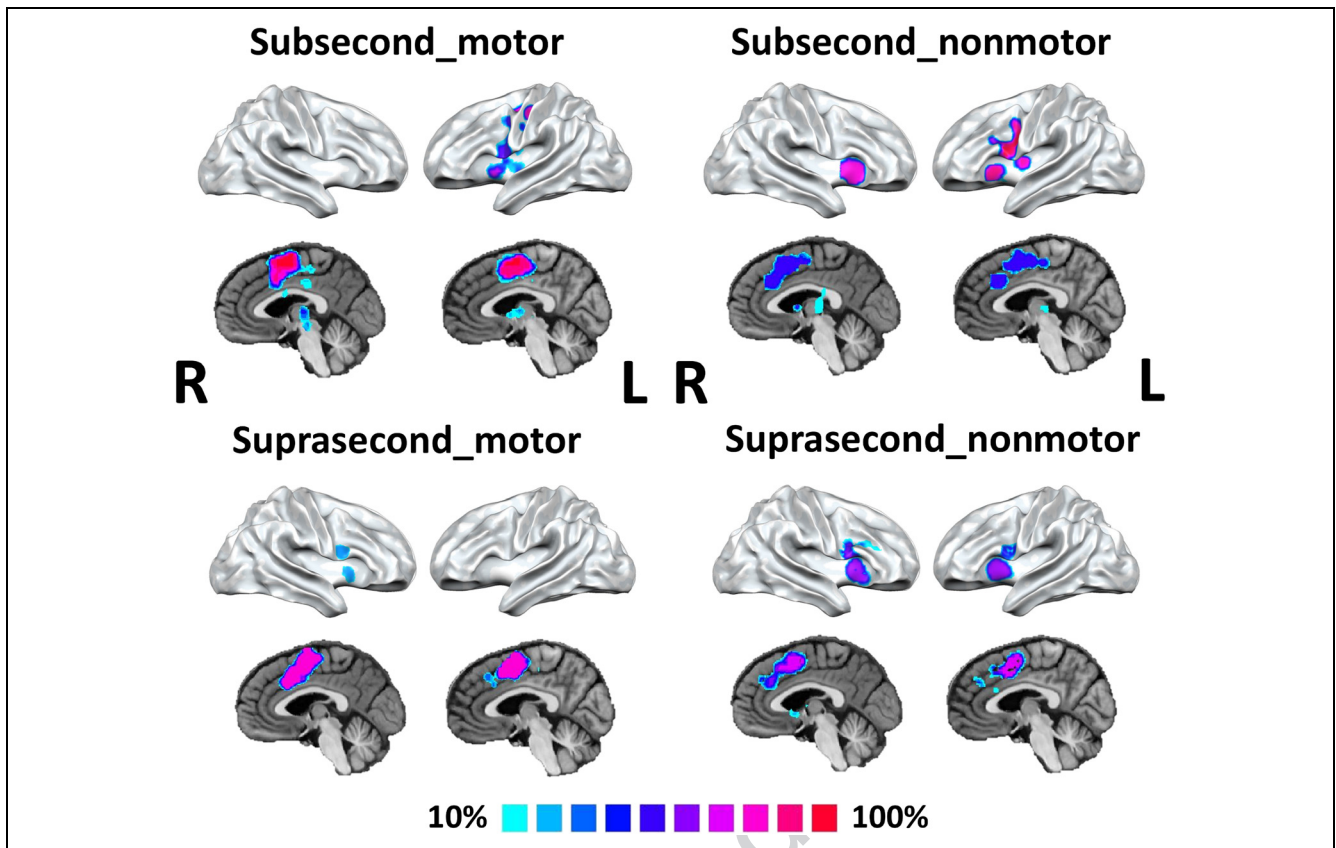


Figure 7. Results of the fail-safe analyses for the four conditions. Colors from light blue to red represent increasing resistance to injected noise. Slices on the axial plane are shown in radiological convention (i.e., right is left, left is right).

Motor and perceptual conditions have similar profiles, but the pattern associated with the motor condition is more extended in subcortical and parietal sites than the pattern associated with the perceptual condition. The recruitment of parietal sites is probably due to the well-known functions of these cortical areas in the elaboration of the *where* and *how* of spatial vision (Oliveri et al., 2009; Alexander, Cowey, & Walsh, 2005), which are fundamental for building spatiotemporal representations and then voluntarily orienting the motor response (but see further on for a more detailed discussion of this point).

Overall, our analysis provides evidence that the patterns associated with the four conditions are characterized by many common activations in cerebral sites; in particular, they share activations in the following regions: the insula, superior, medial and inferior frontal gyri, precentral gyrus, cingulate gyrus, superior temporal gyrus, claustrum, putamen, and caudate body. This various set of brain areas highlights the importance of the interplay between cortical and subcortical components, especially of frontal insular areas and the striatum, in performing tasks related to time (Wittmann, 2013; Wittmann & van Wassenhove, 2009).

The insular cortex is thought to integrate different signals originating from the outside world and within the organism, a function that is fundamental for building an

interoceptive feeling of the state of the body (Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004; Craig, 2002). This integration would rely on an accumulation mechanism of physiological changes in the posterior insula (Wittmann, Simmons, Aron, & Paulus, 2010) and then proceed in sequential representations of homeostatic states in a posterior-to-anterior progression (Craig, 2009b; Singer, Critchley, & Preusschoff, 2009). This would result in a unified metarepresentation capable of forming our internal feelings moment after moment, the development of which would be at the basis of our inner experience of duration (Craig, 2009a).

Undoubtedly, the great involvement of the frontal cortex (superior, medial, middle, and inferior gyri) in all the four conditions points, as already suggested, to the relevance of higher order cognitive processes, such as attention and working memory, to perform time estimation tasks, which in terms of cognitive resources are quite demanding (Radua et al., 2014). In particular, the SMA (which corresponds to parts of the superior and medial frontal gyri) has been variously associated with both sensory and sensorimotor processing of temporal intervals, with the rostral SMA (or pre-SMA) more engaged in sensory, nonsequential and suprasecond temporal processing, and the caudal SMA (or SMA-proper) more engaged in sensorimotor, sequential and subsecond temporal processing (Schwartz et al., 2012). Recently a study by Protopapa

et al. (2019) has suggested that the entire SMA may codify chronomaps in a progressive way, with the spatial progression following a typical rostro-caudal direction, with anterior activations (those of pre-SMA) more associated with the processing of shorter time periods, and posterior activations (those of SMA-proper) more associated with the processing of longer time periods. As can be seen by the SMA activations illustrated by Figure 7, our results further support the rostrocaudal gradient proposed by Schwartz et al. (2012), who associate the activity of the pre-SMA and SMA-proper not only to the elaboration of different duration of time intervals but also to different tasks. Our results provide evidence for this view, as the gradient in the activation of the SMA appears to be associated not only with the length of the interval but also with the nature of the tasks, as caudal activations seem to be more related to the motor condition whereas rostral activations seem to be more related to the nonmotor (or perceptual) condition. This finding is also in line with what was reported by Wiener et al. (2011).

The activation of the precentral gyrus, especially the left one, may be related to information rehearsal (Rao et al., 2001) and directed attention (Tzourio et al., 1997). As already observed by Wiener et al. (2010), this area would be involved in maintaining task-directed attention. Furthermore, parts of the precentral gyrus may differ with respect to functional specificity: The equivalent location of the hand area on the motor homunculus may be associated with sub-second tasks, whereas the equivalent location of the mouth site may be associated with suprasedond tasks. In particular, subsecond tasks might engage the precentral gyrus in real (or imagined) timed hand movements (Oullier, Jantzen, Steinberg, & Kelso, 2005), whereas suprasedond tasks might engage this area in vocal (or subvocal) counting strategies (Hinton, Harrington, Binder, Durgerian, & Rao, 2004).

The cingulate cortex, in turn, lies at the crossroads of emotion, sensation, and action. In particular, the ACC is largely connected with the anterior insula, and both areas are essential parts of the salience network (Seeley et al., 2007); therefore, it might support the implementation of attentional and executive control in temporal tasks.

As already seen, the striatum has been repeatedly related to time perception. In virtue of its many connections with cortical regions, this subcortical structure would play the role of an “internal clock” capable of integrating the oscillatory cortical activity. More specifically, the striatal beat frequency (SBF) model proposed by Matell and Meck (2000, 2004) suggests that synchronized frequencies of large cortical areas are the neural inputs constituting the time code for constructing temporal representations. According to the SBF model, the dopaminergic system gives a burst of dopamine to the striatum, thus providing the onset signal for timing a certain stimulus (Meck et al., 2008). The spiny neurons of the striatum would then detect the concurrent activity of specific beat patterns of cortical fluctuations. Our results provide further support for the SBF model. Contributions of the striatum

are in fact present in all the activation patterns associated with the four conditions of temporal processing.

Activity in the superior temporal gyrus has been related to temporal discrimination and reproduction of auditory stimuli (Jahanshahi, Jones, Dirnberger, & Frith, 2006; Rao et al., 2001; Sakai et al., 1999), as well as to the generation of rhythms learned through the auditory modality (Bengtsson, Ehrsson, Forssberg, & Ullen, 2005; Lewis, Wing, Pope, Praamstra, & Miall, 2004; Jancke, Loose, Lutz, Specht, & Shah, 2000; Rao et al., 1997). This region, therefore, plays an important role in the timing of auditory stimuli (Buetti, van Dongen, & Walsh, 2008). However, it has also reported activity in this area in the temporal discrimination of visual stimuli (Coull et al., 2004; Ferrandez et al., 2003). As suggested by the authors of these studies and given that the evaluation of temporal intervals is more difficult for visual than for auditory stimuli (Westheimer, 1999), activation of the superior temporal gyrus may support an auditory imagery strategy or subvocalization, which could help discriminate visual durations.

An interesting finding that has not been reported by previous meta-analyses about time perception, with the exception of Wiener et al. (2012), is the contribution of the claustrum. Activations of this region, whose exact function still remains an unresolved mystery, are present in every pattern associated with the four experimental conditions. The claustrum has many distributed connections to practically all the cortical areas (frontal, premotor, motor, ventral temporal, entorhinal, ventral anterior cingulate, visual, somatosensory, and olfactory), as well as to important subcortical structures (lateral amygdala, putamen, caudate nucleus, and globus pallidus; Baizer, Sherwood, Noonan, & Hof, 2014; Mathur, 2014; Torgerson & Van Horn, 2014). In virtue of these extensive projections, Crick and Koch (2005) proposed that the claustrum might integrate different sensations into a unitary conscious representation. This proposal has been further developed by Smythies, Edelman, and Ramachandran (2012, 2014), who put forward a detailed hypothesis of how the claustrum might bring about this temporal integration. According to this hypothesis, the claustrum may serve as a “synchrony detector,” thus capable of elaborating higher order temporal patterns to coordinate and bind information coming from all over across the brain. Of note, our analysis shows that the claustrum has significant activations in the perceptual conditions. This provides further evidence that the claustrum might play an important role in constructing the temporal infrastructure of consciousness or, as we prefer to call it, the property of consciousness of being a “temporal glue” capable of binding different percepts in a coherent conscious scene. If the claustrum is to be seen as having this role, there seems to be in the brain two regions that are supposed to be “synchrony detectors” for temporal patterns (i.e., the claustrum and the SBF). We do not think that this situation is contradictory, but

rather, we think that data can be reconciled if we consider, as we have noted, that the claustrum is much more activated in perceptual (and cognitive) tasks whereas the striatum appears to be more involved in motor tasks. The two “synchrony detectors” may, therefore, work in synergy with the prevalence of either one or the other according to the nature and demands of the current task.

Another difference with previous meta-analyses is the absence of the cerebellum in three of the activation patterns associated with the temporal conditions. In past studies, the cerebellum has been related to the elaboration of temporal information (Mangels, Ivry, & Shimizu, 1998; Jueptner et al., 1995; Ivry, 1993; Ivry & Keele, 1989). More recently, the cerebellum has been linked to the processing of duration-based rather than beat-based intervals (Cope, Grube, Singh, Burn, & Griffiths, 2014; Grube, Cooper, Chinnery, & Griffiths, 2010). Furthermore, it has been proposed that it could play a role in the neural network capable of timing short intervals, as it has been found to be more involved in subsecond rather than in suprasecond tasks (Fierro et al., 2007; Koch et al., 2007; Lee et al., 2007). The label-based meta-analysis carried out by Lewis and Miall (2003a) has confirmed the involvement of cerebellum in time processing. In particular, the authors found the activation of the right cerebellum in subsecond tasks and the activation of the left cerebellum in suprasecond tasks. The review of Penney and Vaitilingam (2008), which also maintained the division of experiments between subsecond and suprasecond categories, found that the cerebellum was the most frequently activated structure in subsecond timing tasks. But as pointed out by Wiener et al. (2010), this review included activations that were subtracted both from control tasks and from the rest condition, thus making it difficult to distinguish between activations related to timing procedures or to other cognitive processes. Finally, Wiener et al. (2010) reported the cerebellum to be active in the subsecond category only. Our results confirm in part the findings of these meta-analyses. As already said, activations of the cerebellum are totally absent in three of the four conditions taken into examination here, save for the subsecond motor. A possible explanation for this result is that the other meta-analyses have probably used less restrictive statistical thresholds. In fact the cerebellum was clearly present only in our unthresholded ALE maps, which suggests that beyond a certain statistical threshold its activation becomes nonsignificant. On the other hand, this result may be more likely due to the large sample of studies used in this meta-analysis. Although all the selected studies conducted whole-brain analyses, not all of them reported activity in the cerebellum. More specifically, the activation foci of the cerebellum found by experiments were as follows: For subsecond motor, 19 (79%) reported activation foci, and 5 (21%) did not. For subsecond perceptual, 13 (52%) reported activation foci, and 12 (48%) did not. For suprasecond motor, 13 (38%) reported activation foci, and 21 (62%) did not. Finally, for suprasecond

perceptual, 9 (35%) reported activation foci, and 17 (65%) did not. In light of these data, the cerebellar activity does not seem to be so relevant as to contribute effectively to the processing of timing tasks that do not pertain to the subsecond motor condition.

Another result of this meta-analysis that contrasts with previous findings is the activation of the parietal cortex. Lewis and Miall (2003a) found this region activated in suprasecond tasks, whereas Wiener et al. (2010) reported activations of this area (especially the inferior parietal lobe) in subsecond motor, subsecond perceptual and suprasecond motor tasks, but not in suprasecond perceptual tasks. Contrary to Lewis and Miall (2003a) and in partial agreement with Wiener et al. (2010), we found activations of the parietal cortex in subsecond and motor tasks only. The activations were mainly restricted to the inferior parietal lobule, with the exception of the post-central gyrus. These findings support the idea that the parietal cortex, in particular the inferior parietal lobule, could play a role in estimating time; however, what it does exactly remains unclear. Leon and Shadlen (2003) found activation of the posterior parietal cortex (i.e., lateral inferior lobule) of macaques in subsecond tasks. On the other hand, Oliveri et al. (2009) applied TMS on the parietal cortex to test healthy participants and patients with right brain damage during a task requiring setting the midpoint of a time suprasecond interval. The authors found that inhibition of the right posterior parietal cortex induces a directional bias in the time bisection task. In turn, Vicario, Martino, and Koch (2013) applied to two groups of healthy adults a transcranial direct current stimulation (anodal, cathodal, or sham) over the left and right posterior parietal cortices and compared the performance of the groups in suprasecond time reproduction tasks. Results showed that, when cathodal stimulation was applied to the right posterior parietal cortex, the temporal accuracy was affected and led participants to overestimate time intervals, whereas when it was applied to the left posterior parietal cortex, the variability in reproducing temporal intervals was reduced. The authors reported no effect for the anodal stimulation. As functions of the parietal cortex are intimately associated with attentional direction and spatial processing, it is extremely difficult to separate these components in timing tasks. The hope is that in the future better devised experimental protocols could help distinguish the contributions of parietal regions to time processing on the one hand and to spatial and attentional processes on the other.

The correlation analysis between the four experimental categories reveals that the strongest couple is subsecond perceptual and suprasecond perceptual, followed by suprasecond motor and suprasecond perceptual, subsecond motor and suprasecond motor, and subsecond motor and subsecond perceptual. In other words, the patterns of activations associated with the perceptual conditions exhibit a greater similarity than the patterns

of activations associated with the motor conditions. These results further suggest that the frontal components, which are predominant in the perceptual conditions, are more specific for the nature of the task rather than for time duration. Furthermore, the subdivision between motor and perceptual processing may be due to the fact that these two conditions rely on different functional patterns of frontal sites, which in part have common activations, as it is also suggested by the VCC analysis, which shows that a variety of frontal voxels contribute to the correlations.

The hierarchical clustering analysis confirms the correlation results, as it shows that the highest similarity is between sub- and suprasecond perceptual conditions. Also the result that the suprasecond motor condition is slightly more similar with the suprasecond perceptual condition is in line with the correlation analysis (according to which the more correlated second couple is suprasecond motor and suprasecond perceptual). This may indicate that the similarity is mostly guided by the frontal components, which are predominant in the suprasecond perceptual condition.

The IG analysis gives us the areas in which we can observe the major differences in peak activation between the four conditions. Interestingly, 13 of 19 areas are localized in the left hemisphere, and among those, most are frontal regions, which suggests that part of the left frontal pattern may have the role of discriminating tasks in each condition.

Finally, different from the meta-analysis of Wiener et al. (2010), which found only two areas (i.e., the SMA and the inferior frontal gyrus) with significant activations in a conjunction analysis of all the timing conditions, our overlap of the patterns of activations obtained with the ALE maps associated with the four conditions reveals just the SMA as the area of 100% of overlap. This provides further evidence for the pivotal role of the SMA in estimating time intervals, independent of the condition.

The SMA, along subcortical structures and the insula, are the areas that survive better the fail-safe procedure. These brain regions, therefore, might be considered as core network nodes for time perception, thus suggesting that our sense of time could emerge from the complex interaction of higher order and automatic cognitive processes.

Limitations and Future Directions

A concern with the ALE approach, which is, however, one of the most applied methods in coordinate-based meta-analyses, is that results might be driven by few experiments, thus representing a particular case among the ones selected for the meta-analysis rather than an overall descriptive view. Still, it should be observed that a minimum amount of 20 experiments is generally considered to be sufficient to avoid this issue (Eickhoff et al., 2016), so that analyses on large databases, as the one carried out here, should not be biased. Also, our sample is very well balanced, as we performed our analysis on a comparable

sample size for each condition. However, although we were able to identify a considerable number of studies, others could have been omitted.

Future studies are needed to unravel the brain mechanisms at the root of our perception/construction of time. We need especially better protocols so as to distinguish in more details the roles played by cerebral structures in temporal processing. For instance, the activity of primary sensorimotor areas might be merely due to real or imaginary counting strategies. It is therefore fundamental to understand in what degree the areas responsible for sensory perception and motor ideation and execution contribute to the estimation of time per se. Finally, whether or not the cerebellum should be considered an essential brain structure in time processing is still a moot point, as it does not show concordance across studies. Our results suggest that its involvement is associated with the subsecond motor but not with the other conditions. Further analyses are needed to address this interesting issue.

Conclusion

The variability of time perception models may be accounted for by the peculiar nature of temporal phenomena, which are not directly related to objects in the outside world and for which we do not possess a dedicated sensory organ. This meta-analysis provides evidence for the existence of specific patterns of activations that can be associated with the perception and/or estimation of time in subsecond and suprasecond motor and nonmotor tasks. These patterns, however, are not radically different but have in part similar profiles of activations, as they share the contributions of common brain areas. Motor and subsecond tasks recruit slightly more contributions of subcortical structures than perceptual and suprasecond tasks, which in turn show patterns of activations more associated with cortical areas. All the conditions, however, exhibit a strong component of frontal areas and, in particular, a robust activation of the SMA. Rostral and caudal parts of this area play a pivotal role in discriminating not only different time intervals but also in relation to the nature of the task conditions. The SMA, in addition with the striatum (especially the putamen) and the claustrum, might constitute a core circuit in the different networks engaged when the sense of time is constructed by the brain.

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Uncorrected Proof