Coordinate-Based Meta-Analyses of the Time Perception Network

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Abstract

The study of time perception has advanced over the past three decades to include numerous neuroimaging studies, most notably including the use of functional Magnetic Resonance Imaging (fMRI). Yet, with this increase in studies, there comes the desire to draw broader conclusions across datasets about the nature and instantiation of time in the human brain. In the absence of collating individual studies together, the field has employed the use of Coordinate-Based Meta-Analyses (CBMA), in which foci from individual studies are modeled as probability distributions within the brain, from which common areas of activation-likelihood are determined. This chapter provides an overview of these CBMA studies, the methods they employ, the conclusions drawn by them, and where future areas of inquiry lie. The result of this survey suggests the existence of a domain-general "timing network" that can be used both as a guide for individual neuroimaging studies and as a template for future meta-analyses.

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Introduction

"Time" is ubiquitous, yet timing studies are not. Indeed, for studying the subject, "time" is not one thing. This is because timing studies occupy a diverse landscape of possible experimental task designs (Allman et al., 2014; Vatakis et al., 2018). Temporal discrimination, production, and reproduction can all be used to measure explicit, prospective timing, yet so can (self)paced finger tapping, target anticipation, and oddball detection (Coull & Nobre, 2008). This diversity complicates the pursuit of neuroimaging studies of timing: should we focus on what is common to all timing tasks? Or should we focus on what makes timing varied, labile, and adaptive?

No easy answer exists to this question (Matthews & Meck, 2014; Salet et al., 2022). Yet, there is a richness in the diversity of neuroimaging studies conducted on the study of time perception. For this chapter, I will focus on explicit timing studies. That is, those studies where "time" is the to-be-attended dimension. While studies investigating implicit timing do exist (Wiener et al., 2010a, b), there is a diversity

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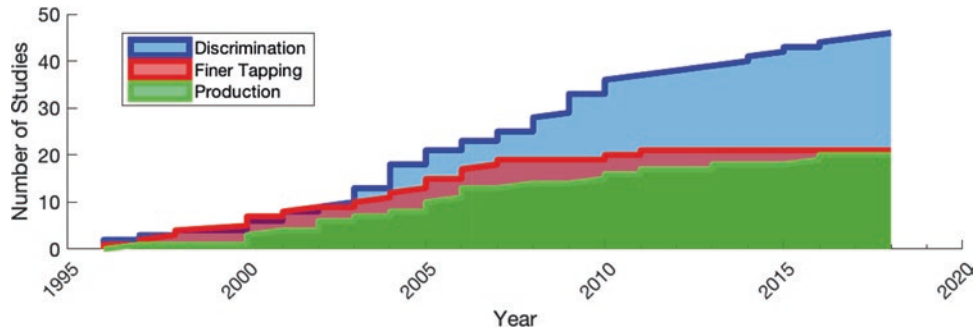

Fig. 1 Two decades of timing studies in neuroimaging. Displayed are cumulative distributions of the number of timing studies for three of the main task designs in time perception: Discrimination, finger tapping, and production. All three studies have increased in prevalence, yet discrimination studies have outpaced the other two types since 2003, whereas the other two main types have plateaued. (Data drawn from (Nani et al., 2019))

among them that may indeed be greater than that found in explicit timing tasks. Part of this is due to the difficulties in building a taxonomy of timing tasks, from which common domains can be determined for inquiry (Paton & Buonomano, 2018; Merchant et al., 2013).

Early attempts in the neuroimaging of time perception highlight the problem in approaching even an area as conserved as explicit timing. Those studies conducted in the 1990s typically focused on paced finger tapping as a measure of timing, which may have grown out of early robust findings in the fMRI literature in examining the neural effects of motor movements (Biswal et al., 1995; Rao et al., 1993). With the advent of event-related fMRI, studies in the 2000s turned to a wider array of experimental designs (Rao et al., 2001), including temporal discrimination and reproduction (Fig. 1). This trend has continued through the 2010s to the present moment this chapter is being written in. Among these newer studies, there have been attempts to examine so-called context effects in time perception (Merchant et al., 2013; Bueti et al., 2008). That is, situations in which time can change as a result of different experimental parameters. This may include the effects of signal emotion, reward, velocity, or magnitude on perceived duration (Matthews & Meck, 2016; Allman et al., 2014). Indeed, beyond finding *where* time can be observed in the brain, these studies highlight attempts to better understand *how* time is encoded (Bueti, 2011). A wider review of these latter studies can be found in other chapters in this volume, but highlight the future of single-imaging studies for time perception, which can include connectionist, multivariate, and encoding-model types.

Coordinate-Based Meta-Analytic Methods

As the neuroimaging literature grew, there were early attempts to provide a better "overview" of findings. Indeed, the exponential rise of fMRI studies led to some concern among researchers for how findings would be concatenated (Fox et al., 1998). This was further compounded by concerns regarding sample sizes in fMRI and the difficult task of determining effect sizes (McGonigle et al., 2000), an issue that is still present today (Grady et al., 2021). Further, concern regarding the generalizability of neuroimaging studies was also present; how certain could researchers be that their findings regarding a particular function would apply to other studies investigating that same function?

To address the above issues, early steps were taken to survey the literature and generate databases of neuroimaging findings. The brainmap database (www.brainmap.org) represents one result of this, in which neuroimaging findings could be categorized and catalogued in a way that other researchers could easily access them as a record (Laird et al., 2005a, b, c). A critical aspect of this was to have appropriate metadata; that is,

terms that could sufficiently describe the functions or tasks of interest for a particular study.

From this effort, the main goal was to provide a way to synthesize results from neuroimaging studies that could provide insight regarding the consistency of findings for a particular area. Up until this point, any attempts at meta-analyses for neuroimaging relied on so-called "label-based" methods, in which activated regions that had been labeled by an atlas were collected across studies and those labels that occurred most often were deemed most likely (Laird et al., 2005a, b, c). This method was useful for describing neuroimaging findings, but suffered from being qualitative in nature. With no statistical test to rigorously interrogate the findings, how certain could a researcher be that the meta-analysis was accurate?

To address this, two primary methods were developed independently yet simultaneously: Activation-Likelihood Estimation (ALE) and Multilevel Kernel Density Analysis (MKDA) (Wager et al., 2009). Both methods were concerned with addressing the *likelihood* of activation for any given brain region associated with a particular function or state [p(activation|function)]. Additionally, both methods relied on using as a starting point the three-dimensional coordinates reported for the peaks of activation clusters in neuroimaging studies. For ALE, the approach sought to answer *what is the probability that a given voxel was active in at least one of the included studies*. To answer this, activation foci from reported studies were all assumed to have an activation probability of 1, but each one was then smoothed with a 3D Gaussian function, such that the probability of activation dropped off in every direction (Turkeltaub et al., 2002; Chein et al., 2002). From there, the sum of these functions was taken at each individual voxel, thus representing the ALE statistic. For MKDA, the approach instead asked how many studies reported activation at a given voxel. To answer this, a 3D uniform distribution of 1 s was spread out in a 10 mm radius from each reported activation foci. These values were then summed across studies, such that the final value represented the number of studies reporting activation at a given location (Wager et al., 2004). One notable distinction between ALE and MKDA values is that the latter provided a more readily interpretable statistic; by looking at any region, one could get a sense instantly of how many studies were reporting activation (Bartra et al., 2013). By contrast, ALE values are in themselves difficult to interpret, as their value will depend on numerous factors, including the smoothing kernel for the Gaussian, the number of foci reported, and the distance between those foci. Yet, an advantage of the ALE method is that the graded probability distributions when summed can provide a *relative* difference in activation-likelihood between different voxels and regions that is more nuanced than MKDA, and so one can thus determine which regions are more likely to be activated over others. Regardless, once generated, both methods provided a similar means of assessing statistical significance, in which a random or null distribution was nonparametrically generated by randomizing the reported foci locations and conducting the generating the ALE/MKDA values again with a high number of repetitions (~10,000). Because both methods relied on producing brain maps from reported coordinates, they were referred to as Coordinate-Based Meta-Analyses (CBMA).

Since the advent of primary CBMA methods, a number of advances have been made as the technique has proliferated (Fox et al., 2014). For both ALE and MKDA, stronger inferences were allowed by providing algorithms for assessing false discovery rate and familywise error, as well as cluster-forming thresholds (Laird et al., 2005a, b, c; Eickhoff et al., 2012). Further work also provided a change from fixed-effects models to random-effects, by incorporating the number of subjects within each study as a covariate to modify individual ALE maps (Eickhoff et al., 2009). Other changes were also made to adjust for errors in the design; for example, both ALE and the original version of MKDA (known as "KDA") were sensitive to studies that reported large number of activation foci compared to those that reported fewer ones. However, updates to both algorithms were able to account for this by restricting their statistics to the likelihood of acti-

vation *across* studies (Turkeltaub et al., 2012). Other additions to the methods allowed for use of subtraction analyses, in which two ALE maps could be contrasted with one another to examine if one type of task was more likely to have activation at a particular voxel than another type of task (Laird et al., 2005a, b, c). All of these additions improved the robustness of CBMA methods, providing stronger inferences regarding brain activation. However, despite these improvements, there are substantial weaknesses to both CBMA approaches. First, and foremost, is that all CBMA methods rely on modeling the uncertainty associated with activation foci. This modeling, once thresholded, provides a map that may appear similar to fMRI activation maps, as both incorporate smoothness into their images. Yet, CBMA methods have no access to the original shape activation, and as such likely do not reflect the "true" activation probability across studies. Indeed, a study that addressed this possibility by comparing CBMA methods to a meta-analysis that incorporated actual statistical maps from a group of experiments found that these methods only matched the true activation pattern by 45% (Salimi-Khorshidi et al., 2009). However, it was noted that, of the methods tested, ALE provided the relatively closest similarity. As a second weakness, both ALE and MKDA do not take into account differences in effect size between studies and activation foci (Radua & Mataix-Cols, 2009). Rather, all activation foci are treated equally. Yet, in practice this is never the case, as marked differences in the size of an effect will differ across activation peaks. Finally, a third major weakness is that both methods are biased to include only those studies that were published, which naturally ignores those studies that were not. This so-called "file drawer" problem means that CBMA methods likely inflate the likelihood of true activation. Notably, a method to correct for this in ALE has recently been developed (Acar et al., 2018).

Finally, while outside the scope of this review, it should be noted that many other CBMA methods were developed and used (Wager et al., 2009; Samartsidis et al., 2017). Indeed, the basic principle is such that anyone could generate their own CBMA using similar means kable (Bartra et al., 2013). Of importance to mention is that both ALE and MKDA include *user-defined* sets of coordinates. That is, the person conducting the CBMA is the one responsible for finding the activation foci from the particular studies they are interested in. This stands in contrast to *automatic* meta-analytic methods, the most prevalent of which is by Neurosynth (Yarkoni et al., 2011). In the Neurosynth method, rather than running a CBMA on a given set of coordinates, the algorithm attempts to search across the *entire* corpus of neuroimaging studies in online journals, to scan the text of these papers to find a term of interest to the user (i.e., "timing"), extract automatically the reported activation foci from those papers, and then generate a CBMA of those coordinates like MKDA. However, from here, Neurosynth compares this activation map to the remaining corpus—that is, those studies lacking the term of interest—and compares them with a chi-square test. The result is two different activation maps: one which provides the probability of activation for a given function or state, and the other which provides the probability of a function or state for a given activation [p(function|activation)]. This latter term provides a so-called "reverse inference" map, in which one can attempt to ask if certain regions are more likely to be activated for particular functions (Poldrack, 2006).

Previous Meta-Analyses of Time Perception Networks

The first CBMA of time perception was conducted in 2010 (Wiener et al., 2010a, b). Before that point, three label-based meta-analyses had been conducted. Of these three, each incorporated a different set of studies and reached somewhat different conclusions. Lewis and Miall (2003) suggested that the cerebellum and supplementary motor area (SMA) were the most likely to be activated, whereas Penney & Vaitilingham (2008) suggested it was the cerebellum and right inferior frontal gyrus (rIFG), and (Macar et al., 2002) suggested a range of cortical and subcorti-

cal structures. With the first meta-analysis, these questions were quantitatively addressed by dividing the corpus of timing studies into those that measured explicit timing at subsecond and suprasecond ranges, as well as whether the task was motor (i.e., paced finger tapping, reproduction) or perceptual (i.e., discrimination, estimation) in nature. Here, the findings demonstrated marked differences in activation-likelihood across sub- and suprasecond ranges, with the former more likely to activate subcortical structures such as the basal ganglia and cerebellum, and the latter recruiting more cortical regions. Crucially, across all timing task variations, the SMA and rIFG were found to be the most commonly active.

Following these initial results, a number of other meta-analyses were run, yet each to address different questions. Indeed, a strength of the CBMA method is that it can ask questions of commonality or differences across studies that may be difficult to ask within an individual study. Ortuño et al. (2011) ran an ALE meta-analysis examining explicit timing studies in both healthy control and schizophrenia patients. For the analysis of healthy control subjects, significant ALE values were found in the SMA, left precentral gyrus, basal ganglia, and thalamus, with reduced activation-likelihood in these same approximate regions for Schizophrenia patients. An additional study also compared activation-likelihood between subjects with Attention-Deficit Hyperactivity Disorder (ADHD) and healthy controls performing timing tasks (Hart et al., 2012). Notably, this study employed another CBMA method, known as Effect-size Signed Differential Mapping (SDM; now known as Seed-based d Mapping). In this method, spatial maps are generated that also take into effect the size and sign of the effect (for example, by incorporating reported *t* statistic values for each peak), and so can account for both direction and magnitude. The results of this meta-analysis demonstrated reduced likelihood in left-hemispheric regions including the IFG, inferior parietal, cerebellum, and insula. Additionally, the right dorsolateral prefrontal cortex (DLPFC) was found to vary depending on medication status across studies in ADHD. A similar study employing SDM was conducted by Radua et al. (2014) that incorporated both time perception and cognitive effort (i.e., working memory and attention). Here, a large overlap between time perception and cognitive effort was observed for many cortical regions associated with time, including the SMA, parietal and prefrontal cortices, with exclusive timing likelihood remaining in the basal ganglia. A crucial insight gained from this study is that many of the regions associated with "timing" were likely engaged in multiple, overlapping functions, noting that the specificity of any one region was difficult to assess.

While the results of Radua and colleagues may suggest that numerous areas associated with "timing" are engaged in other processes during a timing task, it should be noted that CBMA can still afford some insights into the functional subdivisions of these areas. For example, a secondary study followed up on the original Wiener 2010 results by conducting an in-depth analysis of the studies likely to activate solely the SMA (Schwartze et al., 2012). Here, by dividing studies up between motor and perceptual components, the authors demonstrated that activation-likelihood shifted along a rostrocaudal gradient, with perceptual timing studies more likely to activate the anterior SMA, also known as the "pre"-SMA, and motor timing studies more likely activate posterior regions of the SMA "proper." Notably, this finding was also observed in the original 2010 findings (Wiener et al., 2011).

With further neuroimaging studies between 2009 and 2019, a second series of CBMAs for time perception have been run. The first, by (Teghil et al., 2019) divided neuroimaging studies of time perception between those that measured activation while subjects timed an exogenous cue (as in a temporal discrimination task, for example) and those that timed an endogenous cue (as in a self-paced finger tapping task, for example). Here, the general CBMA revealed a pattern of activation likelihood similar to the original 2010 results, including the SMA, bilateral prefrontal and parietal cortices, and the basal ganglia; notably absent was the cerebellum in this study. Between internally and externally

driven stimuli, the authors observed that external stimuli were more likely to activate the SMA, rIFG, left precentral gyrus, and insula, suggesting that external stimuli are stronger drivers of time processing than internally based timekeeping.

The second of the "new" studies was conducted by Nani et al. (2019). Here, the authors conducted a more direct replication of the (Wiener et al., 2010a, b) results by dividing studies between sub- and suprasecond and motor and perceptual domains. Importantly, this study also incorporated numerous controls to measure the robustness of results, incorporating the null distribution correction suggested by Acar et al. (2018). Further, the authors measured correlations between ALE maps, as well as a hierarchical clustering to measure similarities. The results of this more conservative meta-analysis nonetheless revealed a similar pattern to the original 2010 findings, yet with a more conserved volume for each region. Notably, the cerebellum and inferior parietal cortices were less likely to be activated overall, with the former only being observed for subsecond motor timing. In terms of similarity, motor and perceptual studies were more similar to each other across duration ranges, yet at the suprasecond range, motor and perceptual timing studies were quite similar. These results supported the original 2010 findings, noting that the overall results had not changed much despite additional studies, and also provided a more nuanced view of the timing landscape.

The third recent CBMA for time perception was conducted by Cona et al. (2021). In this study, timing-related regions were compared to those that were likely to activate space perception and processing, which included spatial navigation, mental rotation, and spatial attention studies among others. Here, the main ALE analysis for time was again similar to the results of both Wiener et al. (2010a, b) and Nani et al. (2019). Between space and time, the former was more likely to activate posterior regions, including occipital and parietal cortices, whereas the latter was more likely to activate anterior regions, including prefrontal cortex, and subcortical regions including the basal ganglia and cerebellum. A conjunction analysis found significant activation-likelihood in the SMA, rIFG, left precentral gyrus, bilateral insula, and inferior parietal cortices. As an additional analysis, these authors examined "gradients" of activation-likelihood within conjunction regions, finding that the SMA, rIFG, right inferior parietal cortex all shifted in activation-likelihood between time and space studies in either a rostrocaudal or dorsoventral direction.

The final and most recent CBMA was performed by Naghibi et al. (2023). In this study, which collected the largest number of neuroimaging studies of timing to date, the authors segregated the studies according to a variety of classifications, including the duration of stimuli, the modality of the stimuli, whether intervals were presented in a sequence or in isolation, whether the task was perceptual or motor in nature, whether subjects were quantifying or predicting intervals, and the nature of the control task. The last comparison was of particular importance, as the choice of control task and its difficulty can have large differences in observed activation patterns (Livesey et al., 2007). As with other CBMA, a similar network of regions were observed; however, the pre-SMA and left anterior insula were the most robust among the different distinctions.

Does a Time Perception Network Exist?

Altogether, the results of the past 10+ years of meta-analyses for time perception have revealed striking consistency (Fig. 2). Indeed, apart from a few areas that have dropped in and out (i.e., cerebellum, parietal cortex), the remaining overall constellation has been fixed. This consistency raises the question of whether or not a true timing "network" exists in the brain. The existence of such a network would be helpful for future neuroimaging ventures of time perception. Indeed, if one already knows *where* activation is likely to be found across any given timing task, then studies can focus more on *how* those regions are involved (Bueti, 2011).

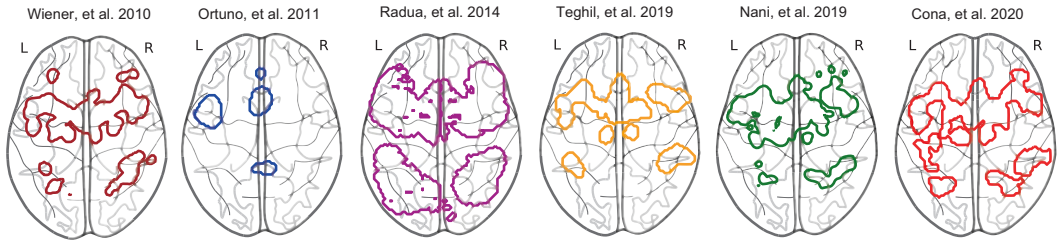

Fig. 2 Timing meta-analyses from 2010 to 2020. From left to right, meta-analyses are presented as contours on a glass brain. The majority of these studies have employed the use of ALE, which changed its methods after 2011. The exception is Radua et al. (2014), which employed Signed Differential Mapping. Across these meta-analyses, a common set of regions can be observed, spanning from the SMA to the basal ganglia, inferior frontal and parietal cortices. Notably, little change has been observed despite the larger number of studies included

In examining the region's most commonly activated across timing meta-analyses, a number of features are readily observed. First, the SMA is consistently the most likely structure to be active across explicit studies of timing. While there are certainly task contexts that influence its function, such as its motor or perceptual nature and spatial context, the region is specifically invoked. Here, then, is our first "node" in an explicit timing network, from which others may diverge. A second area commonly active is the rIFG, spanning pars triangularis and operculum. This region may overlap with the DLPFC, as commonly observed as well in individual studies, yet not commonly reported in meta-analyses. Beyond these two "primary" regions, a number of other nodes are commonly observed across the cortex. These include the bilateral inferior parietal cortices; however, an observed feature is that the right is favored more than the left, with a generally broader distribution that includes the supramarginal gyrus. At the subcortical level, the basal ganglia are also observed bilaterally, including caudate and putamen. Indeed, while these regions may not be commonly observed across *all* timing task variations, it is important to note that the basal ganglia are a set of heterogenous structures, rather than a single unit, and so a lack of activation-likelihood in this region may be due to different studies/contexts activating distinct parts (Wiener et al., 2011). The same context applies to the cerebellum, although here studies are most likely to find activation in subsecond motor paradigms, and most commonly surrounding the dentate gyrus. The thalamus is also commonly observed across neuroimaging studies, although not always as the highest subcortical region. Yet, the thalamus is a critical node for relaying patterns of activity between cortical and subcortical areas; indeed, the striatal beat frequency model of timing (SBF) directly invokes cortico-striato-*thalamic* loops (Matell & Meck, 2004). Finally, stratifying the border between subcortical regions and the cortex are the insular gyri, which are also observed bilaterally. Yet, due to their proximity to the IFG, it is difficult to ascertain at the level of a CBMA if these regions are truly active across timing studies, or merely a result of spreading activation-likelihood from a more lateral cortical source. Regardless, they are included as part of the timing network due to recent work suggesting that interoceptive processes are typically invoked for time processing (Wittmann, 2013).

Altogether, the consensus of timing meta-analyses provides a parcellation that can be called the "Timing Network" (Fig. 3). This network can be used to guide future neuroimaging studies, which can attempt to validate its existence or to further probe interactions between these regions across different task contexts. For example, the edge weights connecting these nodes may vary across different timing tasks or conditions. However, there is still an open question of whether or not a true timing network actually exists. Indeed, among "functional" network parcellations, a number of domain-general networks with distinct yet overlapping activation patterns

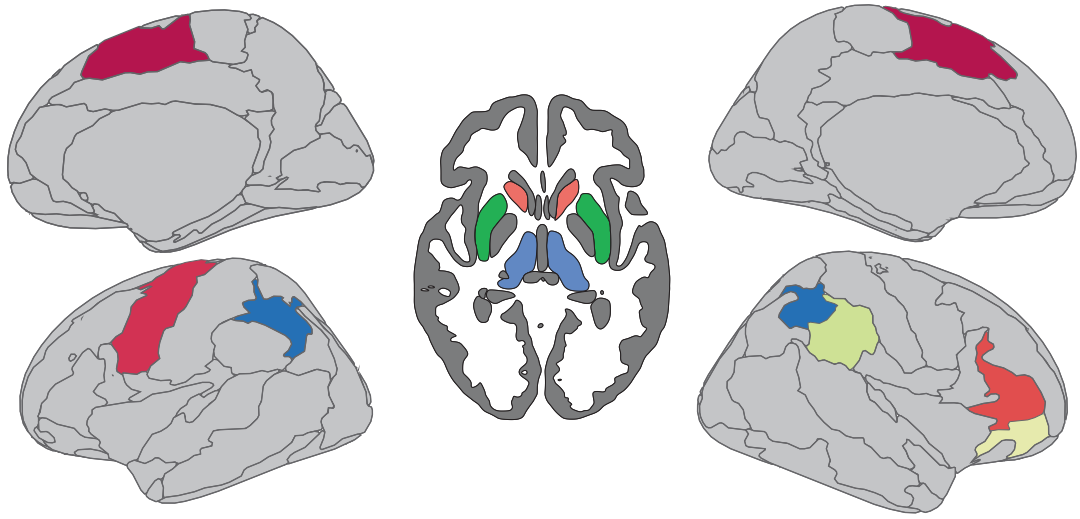

Fig. 3 The proposed timing network. A plot of parcels displayed on a rendered brain, with each colored parcel representing a node in the network. Note that colors here are arbitrary. Each parcel was drawn from the AAL atlas to include those regions most commonly reported across meta-analyses of explicit timing studies. The middle segment includes an axial slice with subcortical structures highlighted. Not displayed here is the cerebellum, which is included in the network. This network is available for download at https://neurovault.org/collections/13081/

are already well-known (Mattar et al., 2015). These include the default mode, dorsal attention, somatomotor, language, cingular-opercular, and multiple demand networks, among numerous others, which will certainly overlap with the proposed timing network. However, the timing network may have a unique collection of regions compared to these others, spanning both cortical and subcortical regions. A true dissociation of these networks from the timing network would require comparisons of structural, functional, and resting-state networks. But, the timing network as conceived here, based on consistent meta-analytic findings, is a reasonable place to start.

The Future of Timing Meta-Analyses

The discussion of prior CBMAs for time perception is meant to highlight two things: (1) the consistency among them for regions associated with time perception, leading to the conclusion of a generalized timing network, and (2) the possibility for future analyses that have not yet been done. Indeed, CBMAs have a strong utility in their ability to address questions of consistency. To that end, there are numerous other possibilities for CBMAs of the timing network that have not yet been employed.

First, among CBMA methods, only ALE and SDM have been used to measure timing networks. This leaves MKDA as a method that has not yet been employed. However, while this may present an opening for a novel meta-analysis, I suggest that the results of MKDA would likely not differ from the prior meta-analyses. This is because, at their core, all CBMA methods rely on the same general strategy for modeling activation based on reported foci (Fox et al., 1998). However, other methods for CBMA exist that may provide at least somewhat divergent findings. One recently developed method, the Analysis of brain coordinates (ABC) shows promise (Tench et al., 2022). Briefly, this method considers at the first-level what *clusters* of studies are most likely to occur across the brain volume, which differs from the ALE/MKDA approach in which clusters are later defined after statistical thresholding. The ABC method further thresholds these clusters based on the expected proportion that would occur by chance. As a result, significant clusters for ABC report clusters

that are likely to *replicate* across the corpus of included studies.

Second, other extensions to the ALE algorithm exist that have not yet been tested. The first is termed Meta-Analytic Connectivity Modeling (MACM) (Laird et al., 2009). MACM is a type of connectivity analysis that shares the same strategy as that used by seed-based connectivity measures. Specifically, MACM works by isolating a particular voxel or region of the brain, and then searching for all studies that report activation for that particular region. Notably, this search may be restricted to only include studies that investigate a particular area (i.e., timing). The activation foci for these studies are extracted and a standard ALE analysis is run, with the resulting MACM map displaying those regions that are significantly associated with the seed region of interest. For example, one could specify the SMA as a node, and then examine all other regions that are commonly activated with it. Comparisons between regions in the timing network may yield details regarding how different regions interact across different task contexts.

While MACM provides a measure of *association,* it is important to stress that it does not provide a measure of *connectivity* in the sense applied to studies of resting-state or task-based fMRI, and even their claims of connections may be spurious (Leonardi & Van, 2015). A closer measure for CBMA is the recently developed Co-activation Probability Estimation (CoPE) method (Chu et al., 2015). In the CoPE method, activation foci are treated as probability distributions, similar to ALE, but with a smaller width. From here, values are normalized and the co-activation of each voxel is measured across studies. That is, which voxels are likely to be activated together across studies? The resulting measures are compared against a null distribution from Monte Carlo simulations for statistical significance, resulting in a map where clusters represent those that are co-active across studies. The important distinction of the CoPE method is that it can distinguish between local and long-range connectivity, and so be used to derive a connectivity matrix between regions. Applying CoPE for time perception would allow for a true measure of network properties observed across studies. Yet, as of this writing, no software package for CoPE is publicly available, limiting its use.

As an alternative to the CoPE method, a more recent CBMA connectivity measure has been proposed, for which a freely available software package exists (Tench et al., 2020). This method, known as Coordinate-based meta-analysis of networks (CBMAN), is a variation of the ABC method described above. Broadly, the CBMAN method works by measuring z-scores associated with reported activation peaks and examining their covariance structure across the included structures. As a result, multivariate normal distributions can be fit to the z-scores of the most likely clusters for activation, with the covariance used to estimate connectivity between clusters. As this method includes both activation foci and effect sizes, it provides a strong measure for inferring connectivity; ripe for the study of timing.

A final, untapped method is to examine reverse inferences for the timing network. That is, up until now, all of the CBMA methods here report the likelihood of activation *given* the set of included studies [p(activation|timing)]. However, they do not speak to the converse inference: what is the probability of a timing task having occurred, given activation is found in a particular region [p(timing|activation)]. For example, if a study finds a significant cluster in the SMA, was the subject timing? Knowing this probability can provide insight into the *specificity* of any one region for timing. However, given the ubiquity of timing studies, it is likely that no single region has a high *absolute* probability for timing, but rather there will be *relative* differences between regions (e.g., if SMA activation is observed, is it more likely that a subject was timing than if right parietal activation is found). As described above, the Neurosynth method provides a means to assess this. Yet, Neurosynth relies on automatic tagging of studies based on terms of interest, and the term "timing" likely includes those studies associated with time perception and those that aren't. In fact, the Neurosynth website does include this term, but with no clear clusters available for reverse inference. However, given the

ALE values represent the forward probability of activation, it is possible via Bayes Theorem to construct the posterior probability. This method has recently been proposed for ALE (Costa et al., 2021), and provides a simple software plugin to accomplish it. The only requirement, however, is to have a set of "nontiming" studies to compare with it.

Recently, we noted this method was employed by our group (Mondok & Wiener, 2022). Here, we employed the timing studies used in our previous meta-analysis (Cona et al., 2021) and conducted the reverse-inference analysis as described above. Two main findings emerged from this analysis. First, the overall probability of a timing task having been conducted, given activation of a particular brain region, was low. Indeed, no single region offered high predictive value for determining if a study was employing a timing study over another task. However, it should be noted that *many* tasks offer low predictive value, especially when a large network of regional activations are possible (Yarkoni et al., 2011). Nonetheless, among those regions that were predictive, the SMA and the bilateral insula had the highest predictive power for timing tasks. In particular, we note an interesting convergence with the recent results of (Naghibi et al., 2023), who in their standard CBMA also found these regions as having the most consistent likelihood.

Conclusions

In discussing CBMA methods and their application for time perception, a final open question is whether or not there are new analyses available at the aggregate level that can yield insights to how timing is accomplished in the brain. Hopefully, the new methods described just above can be applied with important distinctions available, and when carefully applied can provide further details about the existence and flexibility of the timing network. Further, additional methods may come along that provide a new leap in our understanding of time at the collective level. Regardless, the foundation for any meta-analysis is the individual studies that support it. As timing studies continue to be done with neuroimaging, more detailed questions can be asked, and more can be learned.

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