Review

Cognitive neuroscience 2.0: building a cumulative science of human brain function

Tal Yarkoni[1], Russell A. Poldrack[2], David C. Van Essen[3] and Tor D. Wager[1]

[1] Department of Psychology and Neuroscience, University of Colorado at Boulder, UCB 345, Boulder, CO 80309, USA
[2] Departments of Psychology and Neurobiology, University of Texas at Austin, 2935B West Braker Lane, Austin, TX 78759, USA
[3] Department of Anatomy and Neurobiology, Washington University in St. Louis School of Medicine, Campus Box 8108, 660 South Euclid Avenue, St. Louis, MO 63110, USA

Cognitive neuroscientists increasingly recognize that continued progress in understanding human brain function will require not only the acquisition of new data, but also the synthesis and integration of data across studies and laboratories. Here we review ongoing efforts to develop a more cumulative science of human brain function. We discuss the rationale for an increased focus on formal synthesis of the cognitive neuroscience literature, provide an overview of recently developed tools and platforms designed to facilitate the sharing and integration of neuroimaging data, and conclude with a discussion of several emerging developments that hold even greater promise in advancing the study of human brain function.

Science by synthesis

Science is, by nature, a cumulative endeavor. Scientific advances generally build directly on previous studies and issue findings that only make sense in light of existing knowledge. In cognitive neuroscience, as in many other scientific disciplines, a gold standard for scientific progress and accumulation of knowledge has historically been the 'critical experiment': a single empirical test that decisively disqualifies one or more hypotheses from further consideration [1]. Valuable as they can be, however, critical experiments are not the only way to make scientific progress. In fields such as genetics, cognitive science and, we argue, functional neuroimaging, important scientific advances also result from the synthesis and modeling of existing data, in addition to the collection of new data. The overall behavior of a system as complex as the human brain cannot readily be inferred from isolated analyses of a few variables. No single experiment can control for all, or even most, extraneous variables; and even if it were possible to isolate and control a single variable – that is a single brain region or psychological factor – the 'critical experiment' would only allow for very limited inferences about human behavior. In recognition of these basic principles, a trend has emerged across disciplines towards the synthesis of data and modeling of the overall behavior of highly multivariate systems. These approaches build on accumulated evidence from hundreds or thousands of individual experiments, and provide a 'bird's eye view' that complements the traditional experimental approach.

In this article, we review recent efforts to accelerate progress in cognitive neuroscience through greater formal synthesis of the rapidly growing primary literature. We begin by elaborating on the motivation for such an approach by discussing several constraints that limit the ability of individual brain-imaging studies to draw strong inferences about structure–function relationships. Next, we briefly review key historical developments and discuss several currently available tools and techniques for aggregating, organizing and analyzing existing neuroimaging data. Finally, we turn a speculative eye towards the future and discuss potential developments that might accelerate the development of a cumulative cognitive neuroscience.

The rationale

Why is an increased focus on formal synthesis of cognitive neuroscience literature needed? Much of the difficulty in drawing strong and selective inferences about brain structure and function reflects fundamental statistical and methodological constraints that are difficult, if not impossible, for most individual studies to overcome. We focus here on several limitations that can be ameliorated by synthesizing results across many experiments and laboratories.

Most neuroimaging studies are underpowered

Most neuroimaging studies produce maps of brain regions that are activated by some process of interest. When researchers draw inferences about brain–behavior relationships from such maps, they often tacitly assume that these maps provide a relatively comprehensive and accurate picture of the true effects. Unfortunately, this assumption will probably fail in most cases. The small sample sizes (typically 15 – 20 subjects) and stringent statistical thresholds ($P < .001$ or lower) commonly used in fMRI studies might provide little power to detect anything but extremely large effects in many circumstances [2–4]. As a result, many if not most fMRI analyses will detect only a fraction of the true effects, producing a deceptive illusion of 'selective' activation. Moreover, because researchers typically report only those results that attain statistical significance, the effect sizes reported in the literature tend to

Corresponding author: Yarkoni, T. (tal.yarkoni@colorado.edu).

  doi:10.1016/j.tics.2010.08.004

Box 1. Meta-analysis of neuroimaging: goals and techniques

Meta-analysis techniques provide a way of aggregating data across studies and testing the replicability of effects across laboratories, sites and study variants; they are increasingly used to evaluate and synthesize the research literature. For example, recent meta-analyses of drug treatments for depression have explicitly examined publication bias [55], and have called into question the benefits of antidepressants for mild and moderate depression [56,57].

Neuroimaging meta-analyses are typically based on published three-dimensional coordinates for activation locations, with dozens of published meta-analyses of various basic and clinical topics [39,40]. Although a variety of approaches have been used [40], the dominant approaches use kernel-based reconstruction of meta-analytic statistical maps (see Figure 1a and [6,25] for details). Such meta-analyses can serve many functions, a few of which we describe below:

- *Consensus* a priori *regions of interest (ROIs).* Areas such as the 'anterior cingulate' span thousands of brain voxels. Results from prior studies of even narrowly-defined tasks can span broad regions, limiting their usefulness for ROI development. Meta-analysis can provide a consensus specification of precise voxels of interest, reducing multiple comparisons and increasing power.
- *Evaluating psychological specificity.* Quantitative discrimination among psychological states requires comparison of results across many task domains, patient groups and so on. Meta-analysis is uniquely suited for such comparisons. For example, although the amygdala is sometimes considered synonymous with fear, meta-analytic evidence indicates that it is at least as activated for disgust ([53]; Figure 1b).
- *Testing existing hypotheses.* As in other domains, neuroimaging meta-analyses can be used to assess the accumulated evidence for existing hypotheses. Exemplar meta-analysis results include findings that amygdala responses in emotion tasks are left lateralized and are stronger for negative emotion, confirming prior hypotheses [58], coupled with lack of support for right-hemisphere dominance in emotion and limited support for differential frontal lateralization by valence.
- *Establishing correspondence across domains.* Meta-analysis can help establish commonalities and dissociations across task types or patient groups. For example, a recent meta-analysis established common amygdala and insula hyper-reactivity across three kinds of anxiety-related disorders, but found hypoactivity in ventromedial prefrontal cortex only in post-traumatic stress disorder [52].
- *Developing new hypotheses.* Negative emotion is sometimes considered synonymous with the amygdala, but other areas that seem crucial in animal models, such as the periaqeductal gray (PAG) and hypothalamus, are rarely mentioned in human studies. A recent meta-analysis found evidence for replicable activity in human studies of emotion in both regions ([51]; Figure 1c). Such findings can lead researchers to consider the importance of PAG activity in new studies.

be substantially inflated [2,5]. Because pragmatic considerations suggest that sample sizes in most neuroimaging studies will probably remain relatively small, synthesis of results via meta-analysis offers the best way to increase statistical power and, ultimately (via image-based meta-analyses discussed below), better effect size estimates. Moreover, unlike large, highly powered studies of a single paradigm, meta-analysis can capture effects that are consistent across laboratories and task variants (Box 1).

False positive results are prevalent

Because of the large number of comparisons tested in a typical neuroimaging study, even relatively conservative uncorrected statistical thresholds (e.g. $P < .001$) are usually insufficient to adequately control the false positive rate across the entire volume (e.g. the brain). In recent meta-analyses, Wager and colleagues estimated the incidence of false positives among published stereotaxic coordinates ('foci') at approximately 15% – considerably above the conventionally expected 5% level, even with a modal threshold of $P < .001$ [6]. Although individual studies generally cannot distinguish true activations from false positives, meta-analyses can at least separate consistent findings from idiosyncratic ones.

Direct replication is uncommon

A hallmark of the scientific method is its emphasis on replicating findings across different studies. Unfortunately, the high cost of fMRI data collection often precludes direct replication of previous fMRI studies; more typically, researchers focus on 'conceptual' replications that retain features of a previous study while introducing a new manipulation or context. In addition, there is no consensus on exactly what constitutes a replication. In voxel-wise mapping studies, which currently dominate the field, it is unclear how close an activation peak must be to a previously reported one, or how much overlap in activated voxels two maps must share, to count as a replication. These difficulties arise in part because inferences are typically made on whether voxels are activated and not directly on where activated regions are located. Meta-analyses have the potential to ameliorate these problems by defining consensus areas that can be tested in direct replications.

Selective association is difficult to establish

A primary goal of cognitive neuroscience research is to selectively associate particular functions with specific regions or networks. However, the standard cognitive neuroscience strategy of determining which brain regions are associated with a particular manipulation of cognitive function is not well suited for the identification of selective structure–function associations because overlapping brain regions can be reliably activated by multiple psychological functions [7]. To identify truly selective mappings, one must establish both that a specific task consistently activates a given region, and that the same region is not consistently activated by many other tasks [8] – a challenging proposition for any individual study. For example, common assumptions about the mapping between neural and mental activity can be empirically tested using meta-analysis, and often prove to be incorrect – such as the notion that increased amygdala activity is a specific marker of negative emotions such as fear (Box 1; Figure 1).

Formal structure is needed

There is a growing tendency within cognitive neuroscience to move beyond simple brain-behavior mappings, which focus on where in the brain activation is occurring, toward more integrative models that seek to characterize the large-scale functional–anatomic organization of the brain. This shift in focus is reflected, for example, in efforts to identify core networks underlying human cognitive function: for

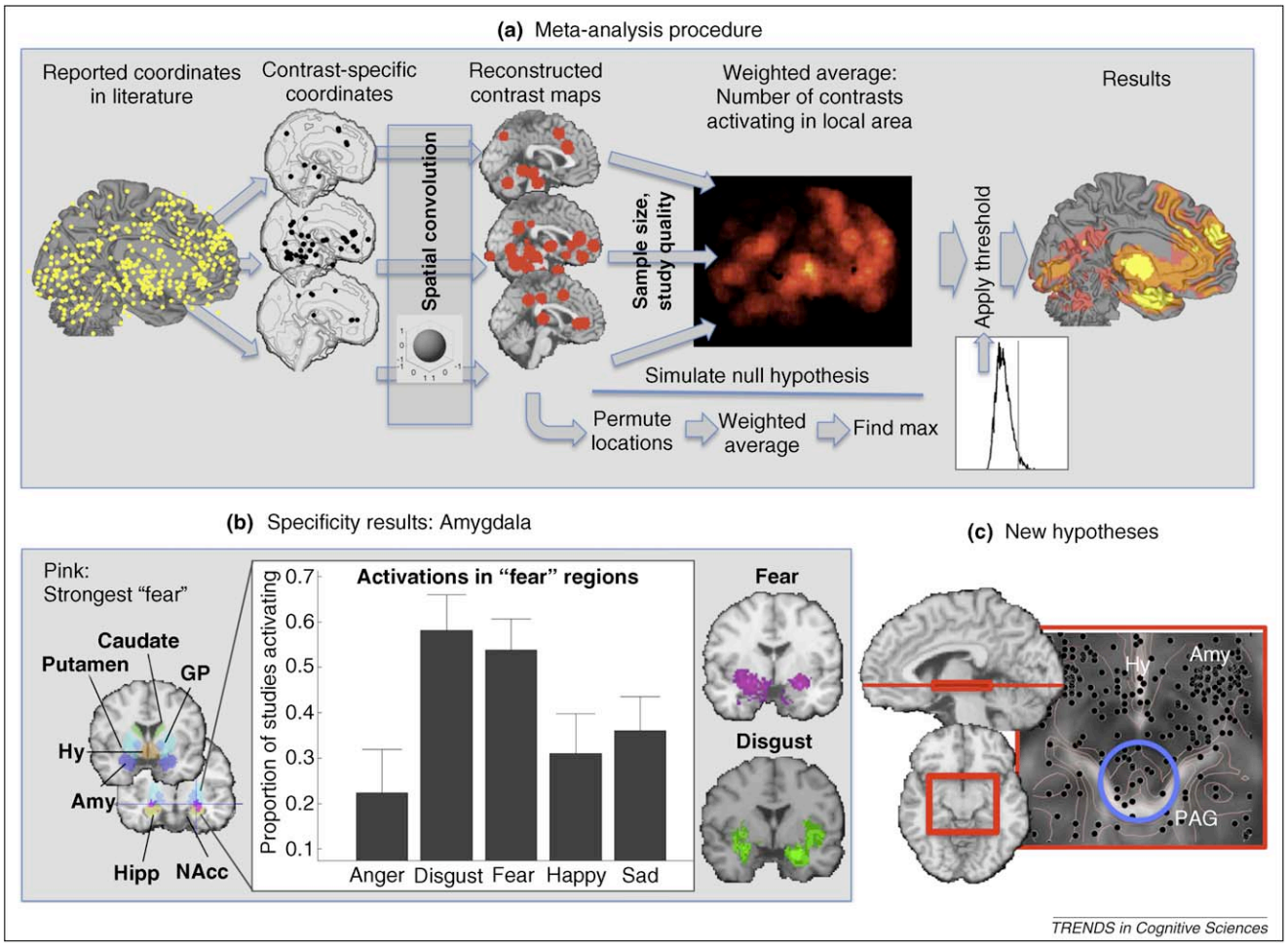

Figure 1. Meta-analysis of neuroimaging data: methods and application. **(a)** Coordinate-based meta-analysis. Whereas early kernel-based approaches were based on simply aggregating coordinates across a set of studies [37,50], recent approaches explicitly test replicability across studies and allow for weighting by sample size and study quality [6,25]. The diagram shows the procedure for one of the newer techniques, Multilevel Kernel Density Analysis [51,52]. Reported peaks are separated by contrast map (often synonymous with study) and convolved with a spatial smoothing kernel. A weighted average map is constructed, considering sample size and other measures of study quality. The map is thresholded by randomizing the locations of the within-study activation regions many times (e.g. 10000) and calculating the null-hypothesis distribution of the maximum across the image. This threshold provides family-wise error rate control, so that any region in the resulting thresholded map can be interpreted as more consistently activated across studies than would be expected by chance. Similar methods are available for comparing two or more task conditions (see [40]). **(b)** Results in the sublenticular extended amygdala (Amy) from a meta-analysis comparing emotional tasks across emotion types (adapted from Table 1 in [53]). Amygdala responses are not specific for fear. **(c)** Results in the periaqueductal gray (PAG), hypothalamus (Hy), and amygdala across studies (adapted from [51]). Replicable activation in the PAG points towards new hypothesis about PAG's previously under-appreciated role in human emotion.

example the 'default' network [9] and the 'task-positive' network [10] – so named for their high levels of activity at rest and responsivity to a range of tasks that require external attention, respectively. The 'core network' approach complements the more conventional focus on isolated brain regions. The introduction of multivariate approaches such as independent component analysis (ICA) [11] and related techniques to the fMRI arsenal have provided researchers with powerful tools for modeling networks. A major barrier to progress, however, is the relative absence of an overarching framework for describing neural and mental function. There is currently little consensus about how to classify or group different brain regions, networks, experimental tasks or cognitive functions, let alone how to develop mappings between different levels of description. Development of suitable descriptive frameworks (or 'ontologies') of cognitive and brain function cannot be accomplished within individual studies that focus narrowly on specific experimental contrasts, and will instead require the formal synthesis of large portions of the published literature.

The methods

Many researchers in the field of cognitive neuroscience increasingly appreciate the importance of conducting formal syntheses of cognitive neuroscience literature. In this section we summarize relevant history and discuss several recently developed tools and platforms designed to facilitate the sharing and integration of neuroimaging data. Our review is by no means exhaustive; it mainly emphasizes what we view as some of the more promising recent developments.

Data aggregation, atlasing and sharing

One way to increase the power and generalizability of neuroimaging studies is to aggregate data across multiple sites and studies [12]. This entails bringing data from different studies into a common spatial framework (an atlas) and a common data format, and also making the data readily available. Over the past two decades, there have been important advances on all three fronts. Many of these advances were fueled by the Human Brain Project

[13], Biomedical Informatics Research Network (BIRN; http://www.birncommunity.org/), and other targeted funding mechanisms in the USA and other countries.

The Talairach atlas and its associated stereotaxic space, which allows for the reporting of stereotaxic coordinates (foci) describing the centers of brain activations or deactivations associated with various tasks, were introduced to neuroimaging in the 1980s [14,15] as a way to compensate for individual variability in brain size, shape and patterns of cortical folding. Efforts to improve alignment and better compensate for variability have yielded a plethora of magnetic resonance (MR)-based atlases (both single-subject and probabilistic) and stereotaxic spaces, thereby posing a fresh set of challenges for comparing results across studies [16–18]. A crucial factor supporting the shift toward greater integration of the cognitive neuroscience literature has been the development of large-scale online databases [17,19,20] that provide support for rapid data mining, visualization, and analysis of stereotaxic coordinates from many studies. Two of the most prominent such databases are the BrainMap database (http://www.brainmap.org) [21,22] and SumsDB (http://sumsdb.wustl.edu/sums) [23,24], each of which contains study metadata and activation coordinates for a sizable proportion of the neuroimaging literature. Both databases contain extensive functionality for searching, retrieving and analyzing neuroimaging data, although they also have somewhat different emphases (e.g. BrainMap interoperates closely with Activation Likelihood Estimate (ALE) meta-analysis software [25], whereas SumsDB has greater support for online and offline visualization [23,26]). The emergence of such databases has greatly lowered the barrier to formal integration of the research literature, giving rise to a proliferation of studies focusing on synthesis of previous findings rather than generation of primary data.

Although stereotaxic coordinates are easy to report and communicate, they constitute a compact but impoverished distillation that belies the spatial complexity and richness of neuroimaging data. An early database infrastructure that could handle the full complexity of imaging data was developed in the 1990s by the fMRI Data Center (fMRIDC), which was devoted to storing and sharing large repositories of primary as well as processed neuroimaging data [27,28]. The fMRIDC faced significant challenges, including infrastructure limitations, the use of seemingly incommensurable experimental paradigms and data formats, and a reluctance on the part of many researchers to freely share their data [19,28]. Although it no longer accepts new contributions, the fMRIDC has inspired other recent developments designed to facilitate multi-site collaboration and data sharing of full image information. These include the XNAT (eXtensible Neuroimaging Archive Toolkit) software platform for the storage and dissemination of neuroimaging data [29], as well as web-based resources such as the Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC) for neuroimaging tools [30] and the Neuroscience Information Framework (NIF, http://www.neuinfo.org/; [31]), which provides easy access to a rapidly growing set of databases, neuroimaging tools and other online resources.

Collaborative efforts to aggregate and share data have also produced several very large, publicly accessible datasets. The recent release of the 1000 Functional Connectomes Project – containing data from over 1400 participants scanned at over 35 sites – provides researchers with a valuable dataset for studying brain function during the resting state [32], and can serve as a model for similar efforts using different experimental paradigms. Additional resources include the OASIS dataset (http://www.oasis-brains.org/; [33]) and the ADNI project (Alzheimer's Disease Neuroimaging Initiative; http://www.adni-info.org/; [34]), and the recently announced Human Connectome Project will soon similarly provide immense amounts of information on brain connectivity in a large population of healthy adults (http://www.humanconnectome.org).

Meta-analysis

Researchers have conducted informal qualitative and quantitative meta-analyses of functional neuroimaging data for nearly two decades [35–38]; until recently, however, published meta-analyses were relatively rare. The recent development of standardized and user-friendly meta-analysis software has led to the rapid adoption of stereotaxic coordinate-based meta-analysis as a primary tool for formal integration of neuroimaging results (Box 1; Figure 1; for review, see [6,39,40]). Meta-analyses combining the results of dozens or even hundreds of studies, often reflecting thousands of discrete activation peaks, have been successfully applied in many areas of cognitive neuroscience, ranging from focal analyses of specific cognitive tasks to large-scale analyses of the emotion literature to characterizations of brain disorders (for a summary, see [40]). Such meta-analyses have generally complemented, and in some cases supplanted, the conclusions drawn in individual neuroimaging studies (Box 1).

Ontology development

To identify relations between brain structure and mental function, it is necessary to describe both in a systematic way. In other fields such as molecular biology and genomics, cumulative progress has relied heavily upon knowledge frameworks known as 'ontologies' that describe the conceptual structure of the domain and provide a basis for the annotation of data within databases [41–44]. Cognitive neuroscience currently lacks such consensus frameworks, and several recent projects have been launched with the aim of developing formal ontologies for cognitive neuroscience. One example is the Cognitive Atlas project (http://cognitiveatlas.org; Figure 2), which leverages collaborative social knowledge building to develop a broad knowledge base that characterizes the state of current thought regarding the relations between mental processes and tasks. At the level of task paradigms, the Cognitive Paradigm Ontology (CogPO) project (http://cogpo.org) is developing a framework to describe the many variable features of cognitive tasks. With regard to neural structure, there is a well-established, albeit incomplete, ontology that is now part of the Foundational Model of Anatomy [45]. All of these efforts are being united under the NeuroLex neuroscience lexicon (http://neurolex.org; [46]), which aims to provide a comprehensive lexicon of terms used in neuroscience.

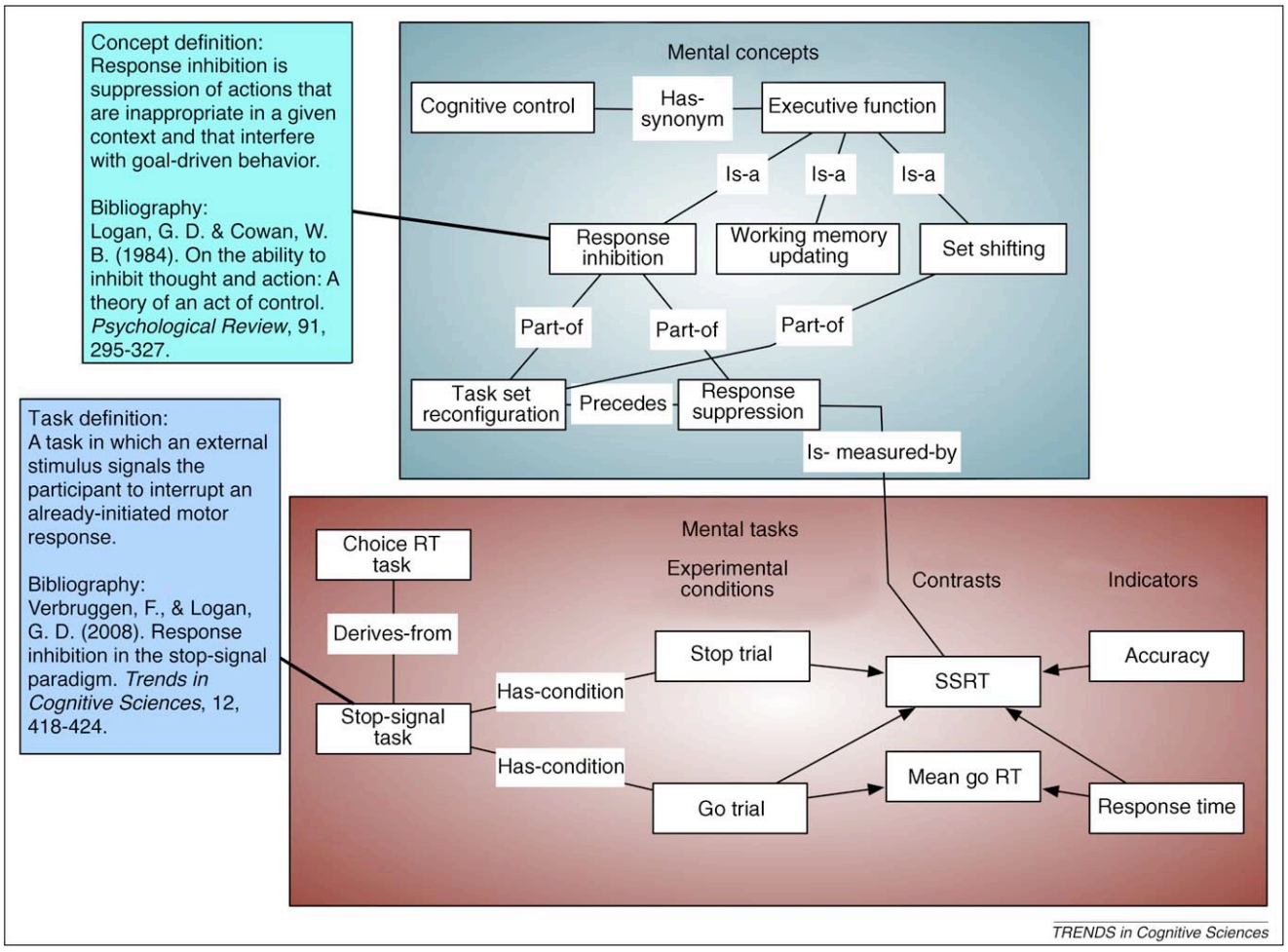

Figure 2. A schematic depicting the structure of the Cognitive Atlas. The Cognitive Atlas (http://www.cognitiveatlas.org) aims to formally represent mental concepts and their relationships to the tasks that are meant to measure them. In this example, a subset of concepts in the domain of executive function is depicted, along with a task (the stop-signal task) that is thought to measure one of these components. Mental concepts (i.e., any process, representation or concept related to mental function) can be related to one another in several ways, including basic ontological relations (such as 'is-a' and 'part-of') as well as temporal precedence relations ('precedes') and semantic relations such synonymy. Tasks are defined in terms of their particular experimental conditions, the contrasts between conditions that generally define experimental effects, and measured variables (called 'indicators'). Specific contrasts (e.g. subtractions between conditions) are related to specific mental concepts by the measurement relation ('is-measured-by'), which formalizes the relations between mental constructs and task manipulations that are often left implicit in cognitive neuroscience research. Tasks can also be related to one another in a family-tree relation (derives-from), which represents the 'task phylogeny' [54] describing the historical evolution of psychological tasks.

The future

The tools and techniques described in the previous section represent, in many respects, only the first steps towards a truly cumulative cognitive neuroscience. Going forward, new tools and technologies will undoubtedly continue to reshape the way cognitive neuroscientists conduct research. Here we highlight several emerging developments that could confer important benefits for the field.

Greater automation and standardization of data reporting and processing

A major limitation of extant coordinate databases and meta-analysis packages is the need for considerable human input at multiple stages of processing. This makes it difficult for databases to keep up with the current literature, let alone incorporate a large backlog of older studies [47]. Overcoming this limitation will require a shift toward greater automation of data gathering and integration. Short-term efforts toward this goal include ongoing development of software supporting the automated extraction of activation coordinates from published articles (Box 2), as well as the introduction of 'best-practice' standards for reporting coordinates in published articles [48]. In the longer term, advances in natural language processing and text-mining could afford automated and machine-readable semantic tagging of studies, facilitating more precise literature searches and eventually perhaps even fully automated large-scale meta-analyses of the literature.

Images, not foci

At present, virtually all formal syntheses of the neuroimaging literature operate on discrete foci rather than continuous whole-brain images. From an analytical standpoint, image-based analyses are unquestionably superior to foci-based analyses because the former preserve the full range of effect sizes in the data, providing a substantial power boost while minimizing selection bias [6,49]. There are, however, two major barriers to widespread adoption of image-based meta-analysis. On the technical side, databases are needed that can store rich image data, not only isolated foci, and provide flexible

Box 2. The evolution of neuroimaging databases

Databases such as BrainMap and SumsDB currently serve a vital role in facilitating synthesis of the neuroimaging literature (see main text), but they also have several important limitations. To extend the functionality of neuroimaging databases and ensure their continued evolution, an informal working group named the NeuroImaging Data Access Group (NIDAG; http://nidag.org) has recently been formed. The broad aim of NIDAG is to promote rapid, open and efficient access to the world's neuroimaging data. Interested neuroimaging researchers are encouraged to join the group and contribute to its ongoing projects. Concretely, NIDAG aims to extend existing databases in several ways, including:

- *Automated extraction and coding of activation foci*. The need for extensive manual entry of information has kept databases such as SumsDB and BrainMap from catching up with the explosive growth of the primary neuroimaging literature [47]. To overcome this limitation, pilot software has been developed capable of automatically extracting foci information and metadata from published journal articles with a relatively high degree of accuracy (http://nidag.org/tools/). To store and serve the extracted data, a 'Neuroimaging Coordinate Warehouse' extension to SumsDB is currently being developed.
- *Enhanced metadata*. Metadata is information associated with neuroimaging results (e.g. reported activation coordinates) that can be used to filter or organize results. Because comprehensive manual annotation of the entire literature is practically impossible, an approach is being piloted that can 'tag' every published article with a set of words or phrases that occur at an unusually high frequency within the article text. The resulting tags can then be used to rapidly identify relevant coordinates in a content-based manner (*cf.* [59]). For example, one can request only coordinates from studies that prominently feature the terms 'language,' 'phonology' and 'lexicon'. Pilot efforts indicate that this simple approach is fast, flexible and effective (http://nidag.org/tools).
- *Image storage*. In the long term, we believe the success of neuroimaging databases will be tied to their ability to store, manage, and serve whole-brain image volumes rather than discrete foci (see main text). Achieving this goal will require extensions to existing databases, as well as the creation of client-side tools (e.g. plug-ins for widely-used fMRI packages such as SPM and FSL) that can interface with and upload images to these databases.

Box 3. What will cognitive neuroscience look like 10 years from now?

The bulk of our discussion focuses on current and short-term developments in cognitive neuroscience. What about the longer term? How might cognitive neuroscientists accumulate scientific results and compare them with new findings 10 years from now? Here is a 'wish list' of some possible future developments:

- Fully automated quantitative mapping between cognitive and neural states. Researchers would upload observed activation maps to a database as input and receive as output probabilistic estimates of the psychological states participants are in: essentially, pattern classification on a large scale. Conversely, one could define a novel psychological state using structured queries (based on well-developed psychological ontologies) and obtain a map of the predicted neural correlates of that state.
- Intelligent preprocessing and analysis pipelines that evaluate the quality of newly acquired neuroimaging data in relation to large databases of existing data and flag problems overlooked by standard quality control tools (e.g. identifying subjects whose multivariate activation patterns are inconsistent with known distributions for the task in question).
- Integration or interoperation of neuroimaging databases with other types of data;.for instance, construction of large, freely accessible functional genomics repositories that combine behavioral measures, structural and functional brain imaging, and genomic data, enabling researchers to construct integrative models that span genes, brain and behavior.
- Deployment of massive data repositories capable of storing and serving raw data from 10 s of 1000 s of neuroimaging studies. Such warehouses could be coupled to high-capacity computing clusters, enabling researchers to conduct large-scale analyses currently beyond the reach of individual labs, and supported by web-based front-ends that allow real-time visualization of results.
- Peer-to-peer data collaboration using distributed authoring and version control systems adopted from open source software development (such as git [http://git-scm.com]). Using these systems, data and code could be shared for each step of an analysis, along with raw data.
- Integration of ontologies and data sharing methods with fMRI analysis software. Each experimental condition in an analysis would be linked to a formal description of the task in a cognitive ontology such as CogPo (http://cogpo.org), with seamless integration of the ontology into the software. The cognitive paradigm would then be linked to the proposed underlying mental processes in a psychological ontology such as the Cognitive Atlas (http://cognitiveatlas.org). Because the necessary metadata regarding the task would be captured in the analysis, this would enable one-click data sharing from within the analysis software package.

search capabilities for the complex metadata needed to describe experimental results (Box 2). On the sociological side, researchers must be convinced that the benefits of freely sharing their images outweigh the costs. These challenges are significant but not insuperable; in the long run, we believe that a shift toward image-based data sharing will offer major benefits to cognitive neuroscience research.

Open cognitive neuroscience

More generally, we see cognitive neuroscience increasingly following an open source model, in which both the data and tools used to generate scientific results are made readily available. This shift is, in many respects, the logical endpoint of current trends discussed in the preceding sections. As bandwidth and storage costs continue to fall, centralized repositories of both raw and processed data will become more practical to maintain and access. Increasing automation of data extraction and visualization, coupled with the development of new metadata standards and image-based data repositories, will make it easier for researchers to locate, obtain and integrate data from multiple sites, fulfilling the promise of greater data sharing that funding agencies such as the NIH have long strived for. In the longer term, we view the development of open platforms for storing, managing and retrieving data as a prerequisite for the development of next-generation tools that will reshape the way cognitive neuroscientists conduct research (Box 3).

Concluding remarks

The explosive growth of human brain mapping over the past two decades has raised important challenges for the field. As the primary literature expands, the need for powerful tools capable of synthesizing and distilling the findings of many different studies grows commensurately.

The present article highlighted the benefits of a synthesis-oriented research strategy and reviewed several ongoing efforts to facilitate greater integration of the published literature. Going forward, such integration will undoubtedly accelerate progress in elucidating the neural mechanisms that support the full range of human thought, feeling, and action in health and disease. There is every reason to push forward energetically on efforts to develop a cumulative science of human brain function.

Acknowledgements

This work was supported by NIH award F32NR012081 to T.Y., NIH awards NIMH R01MH076136 and NIDA R01DA027794 to T.D.W., NIH award R01MH082795 to R.A.P., and NIH award R01MH60974 to D.V.E.

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