Neuroinform (2011) 9:21–38
DOI 10.1007/s12021-010-9083-9

BrainKnowledge: A Human Brain Function Mapping Knowledge-Base System

Mei-Yu Hsiao · Chien-Chung Chen · Jyh-Horng Chen

Published online: 21 September 2010

Abstract Associating fMRI image datasets with the available literature is crucial for the analysis and interpretation of fMRI data. Here, we present a human brain function mapping knowledge-base system (BrainKnowledge) that associates fMRI data analysis and literature search functions. BrainKnowledge not only contains indexed literature, but also provides the ability to compare experimental data with those derived from the literature. BrainKnowledge provides three major functions: (1) to search for brain activation models by selecting a particular brain function; (2) to query functions by brain structure; (3) to compare the fMRI data with data extracted from the literature. All these functions are based on our literature extraction and mining module developed earlier (Hsiao, Chen, Chen. Journal of Biomedical Informatics 42, 912–922, 2009), which automatically downloads and extracts information from a vast amount of fMRI literature and generates co-occurrence models and brain association patterns to illustrate the relevance of brain structures and functions. BrainKnowledge currently provides three co-occurrence models: (1) a structure-to-function co-occurrence model; (2) a function-to-structure co-occurrence model; and (3) a brain structure co-occurrence model. Each model has been generated from over 15,000 extracted Medline abstracts. In this study, we illustrate the capabilities of BrainKnowledge and provide an application example with the studies of affect. BrainKnowledge, which combines fMRI experimental results with Medline abstracts, may be of great assistance to scientists not only by freeing up resources and valuable time, but also by providing a powerful tool that collects and organizes over ten thousand abstracts into readily usable and relevant sources of information for researchers.

Keywords Neuroinformatics · Brain function mapping · Brain-function association model · Literature mining · Information extraction · Knowledge bases

M.-Y. Hsiao · J.-H. Chen (✉)
Interdisciplinary MRI/MRS Laboratory, Department of Electrical Engineering, National Taiwan University,
No. 1, Sec. 4, Roosevelt Rd.,
Taipei 106, Taiwan
e-mail: jhchen@ntu.edu.tw

C.-C. Chen
Department of Psychology, National Taiwan University,
No. 1, Sec. 4, Roosevelt Rd.,
Taipei 106, Taiwan

Introduction

Functional magnetic resonance imaging (fMRI), which measures the blood metabolism resulted from neural activities (Ogawa et al. 1992), is a non-invasive approach for studying human brain function. Due to the increasing popularity of brain research, many data analysis tools, such as Statistical Parametric Mapping (SPM) (Friston et al. 1994), FMRIB Software Library (FSL) (Smith et al. 2004), and BrainVoyager are available to develop brain imaging data sets. However, these data analysis packages provide no tools to interpret the statistics they produce. Instead, scientists have to rely on their own knowledge or other tools to find the meaning of the statistics, such as the anatomical names of the brain areas where significant activation are found and the possible functions of those brain structures.

Furthermore, in fMRI studies, scientists have to read a large number of papers in order to design experiments and must then compare their results with those of other studies. Traditionally, scientists manually update their databases by reading and analyzing vast amounts of literature by themselves, which is extremely time-consuming and labor-intensive. Even when a

scientist is an expert in his own field, it is nearly impossible for him to keep up to date with the rapidly increasing wealth of available publications and findings. Literature mining holds great potential for extracting information and knowledge from these huge bodies of fMRI literature, allowing scientists and researchers to work more efficiently and achieve more in less time than ever before.

For this reason, it is becoming ever more important to combine fMRI experimental results with the available published literature. Here, we present a human brain function mapping knowledge-base (BrainKnowledge) system that combines results from users' fMRI analysis and from the literature. BrainKnowledge not only contains indexed literature references, but also provides the ability to compare experimental data with results derived from the mined literature (e.g., the findings of previously published studies). Four online systems similar to BrainKnowledge are BrainMap (Laird et al. 2005; http://brainmap.org/), SumsDB (http://sumsdb.wustl.edu/sums/index.jsp), AMAT (http://www.antoniahamilton.com/amat.html), and the Brede database (Nielsen 2003; http://neuro.imm.dtu.dk/services/jerne/brede/). BrainMap is the first annotated database for published functional neuroimaging studies. It allows researchers manually to input citation information, experimental parameters, and their results in Talairach coordinates (Talairach and Tournoux 1988) in order to carry out further meta-analysis in similar research studies. However, BrainMap contains no image data, only manually inputted summaries of papers (Barinaga 2003). The Brede database, which has a structure similar to that of BrainMap, provides a function to search for associations between Talairach coordinates and textual data in a functional neuroimaging database (Nielsen et al. 2004). In addition, Nielsen et al. also provide the BredeQuery plugin for SPM to extract and submit coordinates to perform a query in the Brede database (Wilkowski et al. 2009a). However, all of these databases rely on researchers to input data manually. The lack of automatic processing severely limits the scope of these databases and reduces their usefulness. The Brede database itself has had few updates since 2005. Wilkowski et al. (2009b) also provide Skeepmed (Semantic Keyword Extraction Pipeline for Medical Documents;http://neuroinf.imm.dtu.dk/skeepmed/) to search for related abstracts by Talairach coordinates and text input. However, it provides only the abstracts that meet the search criterion and does not return an organized search result. PubBrain (http://www.pubbrain.org/) is a literature-search tool that searches PubMed MEDLINE and can visualize results as a heat-map on a brain to show which brain structures correspond with the query terms in the literature. However, PubBrain contains no experimental data.

In fMRI studies, neuroscientists are most interested in: (1) brain responses to a certain experimental task; (2) the structures of the brain in which these responses occur; and (3) the brain functions implied by these responses. Thus, before analyzing brain activities, our system must first target these three key concepts from the fMRI literature: brain structures, experimental tasks, and brain functions. Presently, however, the automatic extraction of named entities from large amounts of text-based data to be analyzed, such as experimental tasks and brain area, is still difficult (Nielsen et al. 2006). As a result, most researchers must continue to rely on manually inputting information into databases, as is the case with BrainMap and the Brede database. In order to resolve this problem of data entry, in our previous study (Hsiao et al. 2009), we constructed a generalized hierarchical concept-based dictionary of brain functions (also referred to as the generalized hierarchical brain function tree) and had developed an information extraction algorithm for extracting terms that were relevant to brain functions and experimental tasks. The precision and recall of our information extraction algorithm was on par with that of human experts. Such an approach should allow for the processing of a large amount of text-based data in a relatively short period of time and promises to overcome the shortcomings of the manual entry approach. BrainKnowledge is built on an information extraction module and provides interactive co-occurrence models that allow users to view the relationship between the brain structures and functions in a visual map. Each model is generated from over 15,000 extracted Medline abstracts.

In this paper, we will describe BrainKnowledge, which provides concept-based queries organized by brain structures and functions and also mines results to support or explain the experimental fMRI results, and we will present an application example with the studies of affect to illustrate its capabilities. The use of this tool, which combines experimental fMRI results with Medline abstracts, may be of great assistance to scientists by freeing up resources and valuable time, thus enabling these researchers to accomplish more in less time.

Material and Method

System Architecture

BrainKnowledge is a Java-based client system that communicates with a server-side database through Java Database Connectivity (JDBC), and is currently maintained on a machine that runs the Microsoft Windows operating system. BrainKnowledge includes an automated system to download and import PubMed MEDLINE abstracts into the database, which is automatically updated every month.

BrainKnowledge was created from scientific literature on brain activation. We used "("fMRI" OR "functional

MRI" OR "functional magnetic resonance imaging") AND human NOT animal" as keywords to retrieve abstracts from PubMed MEDLINE. In our database, we currently have 15,413 abstracts from 1032 journals dating from 1992 to the present and continue to increase this number every month automatically. Notice that, currently, our system focuses on the fMRI literature. The papers using other neuroimging methods and contain no fMRI studies are not included in our data set. Figure 1(a) shows that the number of abstracts for brain activity studies has grown exponentially over the years. From 15,413 abstracts, we indexed 10,867 brain functions, 1,261 experimental tasks, 27,306 brain structures with Talairach labels in the literature, and 336 of brain structure roles (Fig. 1).

As shown in Fig. 2, BrainKnowledge consists of three major functions. The first function is the extraction of the function-to-structure co-occurrence models and brain association patterns (see the section *Query by Brain Function*) that are related to a queried brain function. That is, a user can select a brain function from the hierarchical brain function tree and retrieve the brain structures that are relevant to the selected function from the literature in the database. The second function is the extraction of structure-to-function co-occurrence models and brain structure co-occurrence models (see the section *Query by Brain Structure*). A user can retrieve brain functions and possible associations that are relevant to the selected brain structures. The third function allows a user to compare the fMRI experimental data with the processed literature in the database (see the section *Integrating fMRI Experimental Data with the Literature Results*). These three functions enable users to extract organized information from the literature and thus to help users associate their experimental results with background knowledge in the field. The core of BrainKnowledge is based on the literature extraction and mining module. This module downloads and extracts information and knowledge from the vast body of fMRI literature. The literature-based extraction and mining module, first and foremost, provides co-occurrence models and association patterns between brain structures and functions. It also contains the integrated graphic user interface, which combines fMRI images and mined literature together into a single comprehensive framework. In addition, if users are interested in any particular function or brain structure, they can retrieve the relevant indexed sentence(s) or detailed abstract information via the abstract preview interface. A reference to the original sentence in the abstract may help minimize misinterpretation of the co-occurrence model.

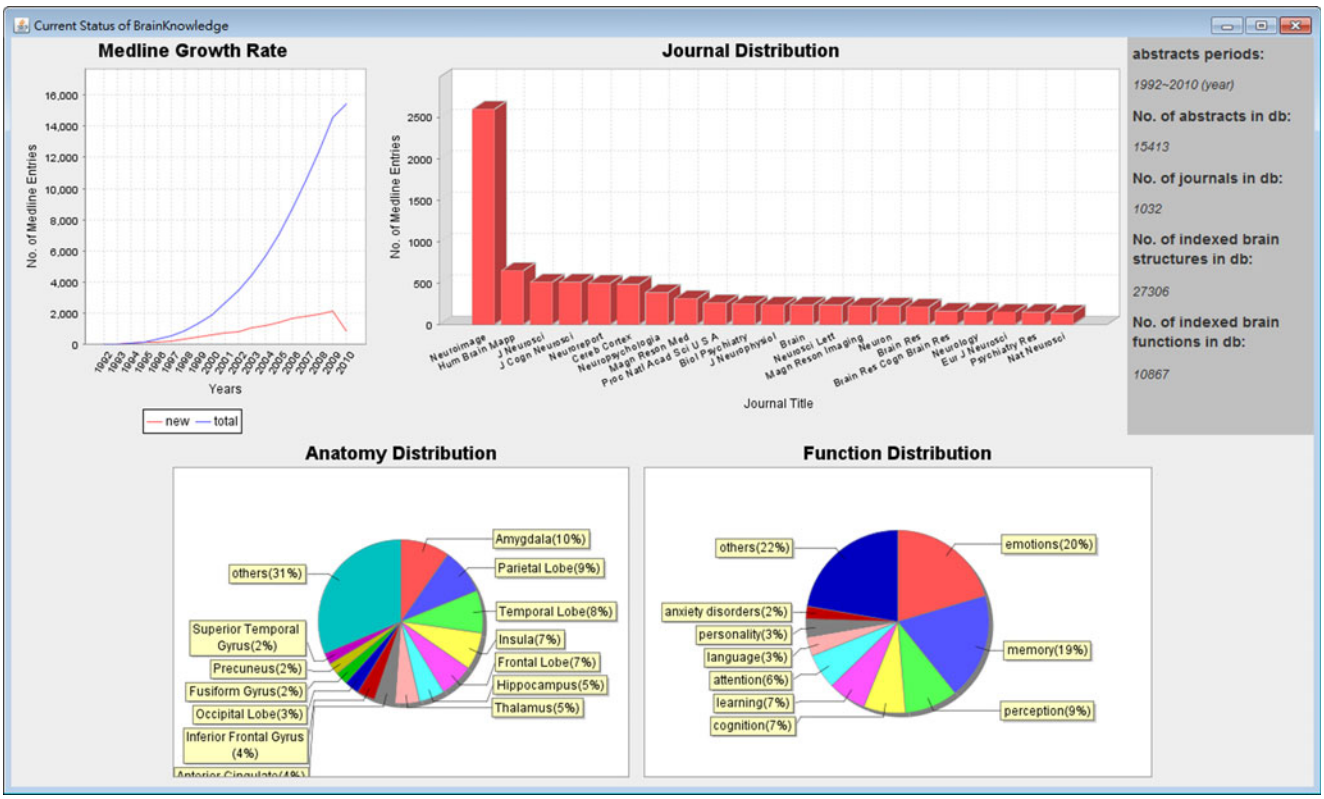


Fig. 1 Screenshot of the current status of BrainKnowledge (statistics panel). **a** the distribution of PubMed MEDLINE growth rates of abstracts that reference "("fMRI" OR "functional MRI" OR "functional magnetic resonance imaging") AND human NOT animal"; **b** the bar chart plots the top 20 journals in BrainKnowledge by frequency; **c** the pie chart shows the proportions of Talairach labels indexed by BrainKnowledge; **d** the pie chart shows the proportions of sorted brain functions indexed by BrainKnowledge

The Core of BrainKnowledge: Literature-based Extraction and Mining Module

The most important information to be gained from fMRI experiments is an understanding of brain activities. For this purpose, we provide researchers with brain-function co-occurrence models and brain structure association patterns mined from various publications. The core of BrainKnowledge is based on the literature extraction and mining module. It is an information retrieval and extraction system that includes an automatic PubMed MEDLINE download and import engine and a named entity extraction module. BrainKnowledge extracts named entities of brain structures, brain functions, and experimental tasks, and retrieves the roles of each brain structure from the literature. The system then uses the extracted information to generate co-occurrence models that provide information about the relationships between brain structures and functions. In addition, we utilized the association mining algorithm to discover interesting patterns from the extracted data.

The PubMed MEDLINE Retrieval and Text Pre-processing Module

MEDLINE is a massive biomedical bibliographic database. We developed an automated system to download and import PubMed MEDLINE abstracts into our database. BrainKnowledge automatically updates the database every month. In BrainKnowledge, we assume that if a brain structure and a cognitive function frequently co-occur in a sentence, there is likely to be an association between the two. Therefore, once new abstracts are received, BrainKnowledge will break them down into individual sentences. Then, by using each sentence as a unit of processing, we extract terms relevant to fMRI experiments by using our named entity extraction module.

The Named Entity Extraction Module

The purpose of the named entity extraction module is to extract a target term from the fMRI literature. The detailed methodology for extracting fMRI related terms was discussed elsewhere (Hsiao et al. 2009). BrainKnowledge extracts brain structure terms with the terms that are in NeuroNames (Bowden and Dubach 2003), a neuro-anatomical thesaurus available in the Unified Medical Language System (UMLS), and in the Talairach atlas (Talairach and Tournoux 1988). The Talairach terms were electronically provided by Lancaster et al. (2000). This limitation is necessary in order to map brain structure terms into brain image templates for visualization (Hsiao et al. 2007). Extracting terms for brain functions and experimental tasks is more difficult as, to the best of our knowledge, there is no publicly available resource on brain function vocabulary that is comprehensive enough for our purpose at this time. Thus, we developed a generalized hierarchical concept-based dictionary (Hsiao et al. 2009) of brain functions for subsequent named entity extraction based on the UMLS, which integrates many terminologies such as MeSH, Psychological Index Terms and similar vocabulary sources. A two-step approach to term recognition and classification was proposed to extract terms related to experimental tasks and brain functions (Hsiao et al. 2009). The first step, term recognition, combines a dictionary and a rule-based approach to identify words that describe experimental tasks and brain functions. The second step, term classification, first uses n-gram approximate term mapping to map the terms to their appropriate concepts, and then assigns them to categories according to our classification rules. Both steps are supported by our brain function dictionary. In addition, in most abstracts, words such as "role" describe the function that a particular brain structure performs. For example, "The corpus callosum plays a 'role' in mediating inter-hemisphere communication." Thus, BrainKnowledge also utilized a rule-based approach, which recognized terms surrounded by specific information items such as "role," to extract brain structure functions.

By using this generalized hierarchical concept-based dictionary of brain function, BrainKnowledge allows users to perform broader concept-based queries; that is, to locate concepts rather than specific keywords. In our dictionary, we merged terms from 23 vocabulary sources to yield more complete coverage than any single source could provide. With such broad, though incomplete, coverage, BrainKnowledge can achieve 72% precision and 73% recall for term recognition, which is on par with human expert performance (Hsiao et al. 2009).

Knowledge Representation

The most widely used model for estimating the relevance of terms is the co-occurrence model. It is the most straightforward and efficient way for researchers to measure how closely connected or related different terms are. The co-occurrence models have been widely applied in biomedical domains, including protein-protein interactions (Ramani et al. 2005; Li et al. 2010), gene-to-gene co-citation networks (Stapley and Benoit 2000; Jenssen et al. 2001; Jelier et al. 2005; Yue et al. 2006; Muller and Mancuso 2008), and cancer-gene relations (Zhu et al. 2007).

In this study, we postulate that when a brain structure and a brain function are frequently mentioned together in the same sentence in a large number of MEDLINE abstracts, there may be an underlying biological relationship between the two. Based on this assumption, we generated co-occurrence models to represent the relevance

of brain structures and functions. BrainKnowledge currently provides three co-occurrence models: the structure-to-function co-occurrence model, the function-to-structure co-occurrence model, and the brain structure co-occurrence model. Each model has been generated from a vast amount of mined Medline abstracts. Note that the co-occurrence models for function-to-structure and structure-to-function contain the same information. The purpose of separating these two models is to provide users with different aspects of the model.

We also used the association mining algorithm to discover interesting patterns from the extracted data. We applied the standard APRIORI algorithm (Agrawal and Srikant 1994) to discover the association patterns of brain structures in different brain function datasets. In our work, an itemset is defined as a set of brain structures. BrainKnowledge calculates the number of sentences in which itemset occurs. If the number of sentences that contain an itemset is greater than a user-defined minimum support, then it is a frequent association pattern. The support of the association pattern is defined as the proportion of sentences with co-occurrence in the data set.

Results

The BrainKnowledge system provides three major functions to help neuroscientists explain and support their findings in fMRI experimental results, as illustrated in Fig. 2. The first function enables the user to perform a brain function query using the hierarchical human brain function tree. The second function enables the user to query brain functions by brain structures. The third function enables users to search for relevant literature by supplying their own analyzed fMRI data. In this section, we will demonstrate the capabilities of BrainKnowledge outlined above, and in the next section we will provide an application example with the studies of affect.

Query by Brain Function

BrainKnowledge allows users to perform a brain function query by keying in a search word or by selecting a brain function term from the hierarchical concept-based brain function dictionary provided by the BrainKnowledge. Figures 3 and 4 show an example of a brain function

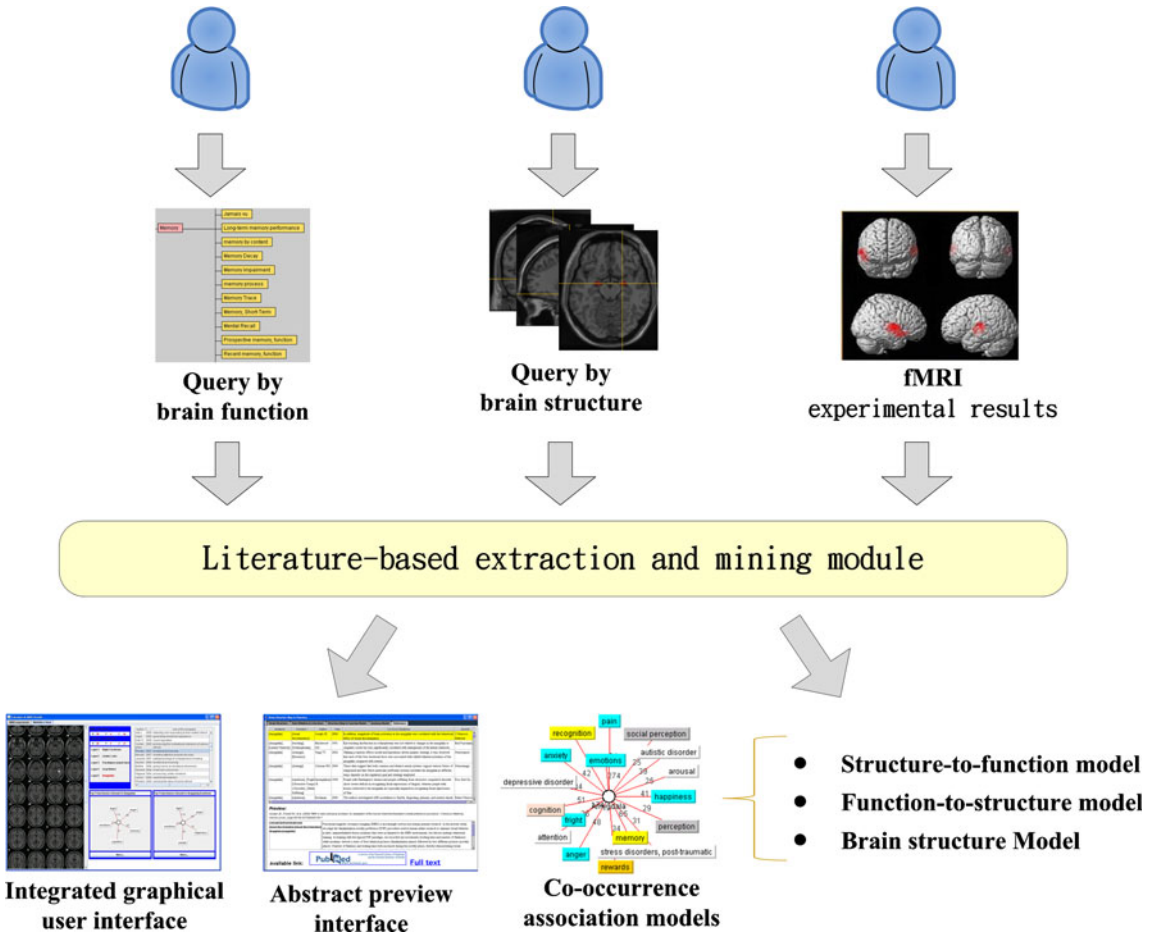


Fig. 2 The conceptual diagram of BrainKnowledge

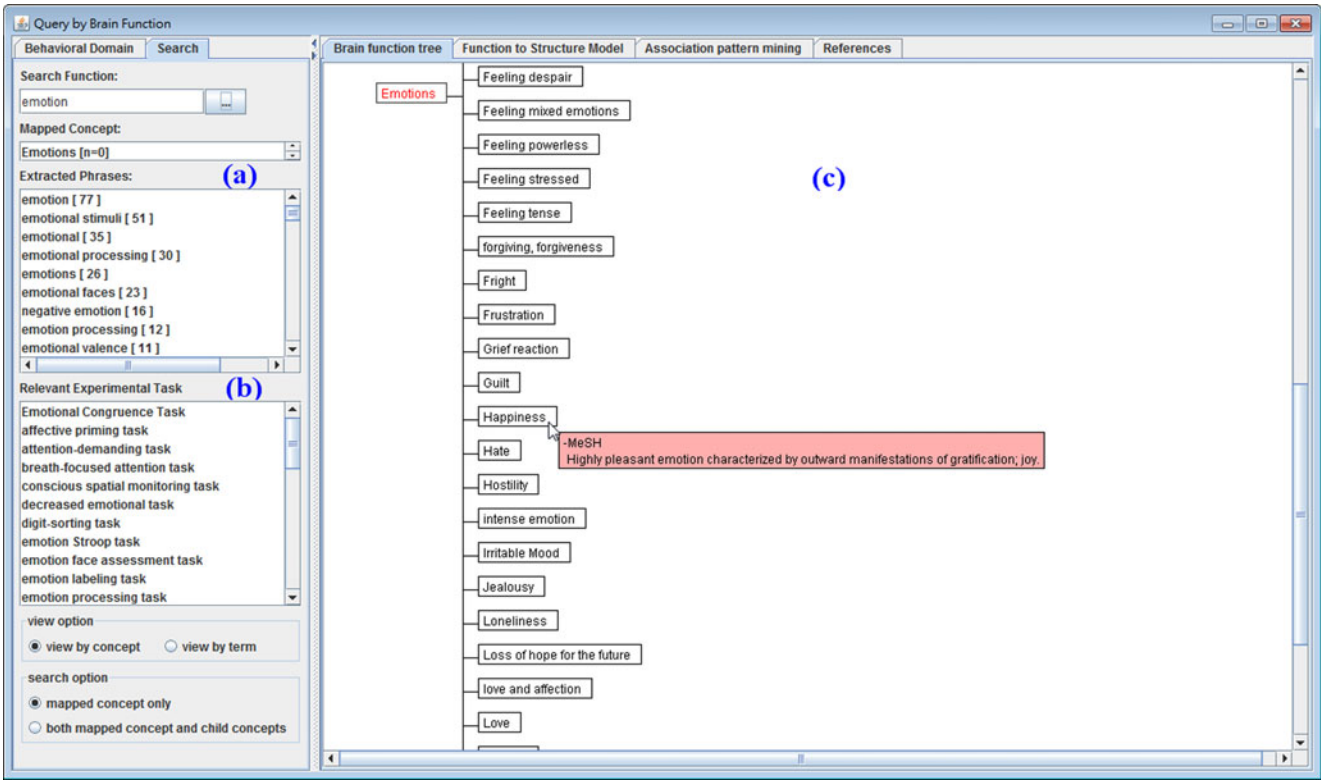


Fig. 3 Screenshot showing the window for querying by brain function. The interface includes 3 tabs showing the brain function tree, function-to-structure model, association pattern mining and references. Here, we perform the brain function query with the search term "emotion": **a** the search panel and the extracted phrases belonging to this concept; **b** list of experimental tasks relevant to the user selected function; **c** the brain function tree (here showing a part of the "emotion" tree); moving the cursor over any term will display definition(s) as defined by the terminologies of UMLS

query. In this example, the user queried for the term "emotion." When a user keys in a search term, BrainKnowledge will map it to the concept of the term and then use this concept to initiate a query from the database. BrainKnowledge then shows all the relevant terms extracted by the named entity extraction module (Hsiao et al. 2009), sorted by the occurrence frequency of the terms. For instance, a query of "emotion" would return terms like "emotional," "emotions," "negative emotion," etc. This information allows the user to refine the search by selecting from the extracted terms.

In addition, BrainKnowledge provides two search options: search by "mapped concept only" and search by "both mapped concept and child concepts." The first option enables the user to retrieve information not only by the search term but also by its concept (synonymous terms). The second option enables the user to retrieve information containing not only the initial search results but also information collected by searching child concepts, as defined in the hierarchical concept-based brain function dictionary. For example, using the system to search for the keyword "emotion" would extend the search to include the concept of "hate," "happiness," "fright," and similarly related terms. Extending the queried terms by means of the hierarchical concept-based dictionary of brain functions provides a broader concept-based query that yields a wider range of data than a normal keyword-based search.

BrainKnowledge returns the relevant experimental tasks, the brain function tree, and the function-to-structure model of the queried brain function. The list of relevant experimental tasks offers scientists a picture of the experimental tasks that had been used in the studies of affect. This will help the scientists find the most relevant literature for result comparison and for the design of future experiments. For instance, for the queried term "emotion," BrainKnowledge would return experimental tasks such as "attention-demanding task," "emotional face-matching task," etc. The brain function tree helps users understand the relationship between the brain functions and their definitions. The brain functions are arranged in a hierarchical structure. A user can click on a function term in the tree to initiate a new search hierarchically. In our example, from the terms returned for the queried term "emotion," the user can click on the term "happiness" in the tree for the refined search related to that term. In addition, moving the mouse cursor over any term will display the definition(s) of that

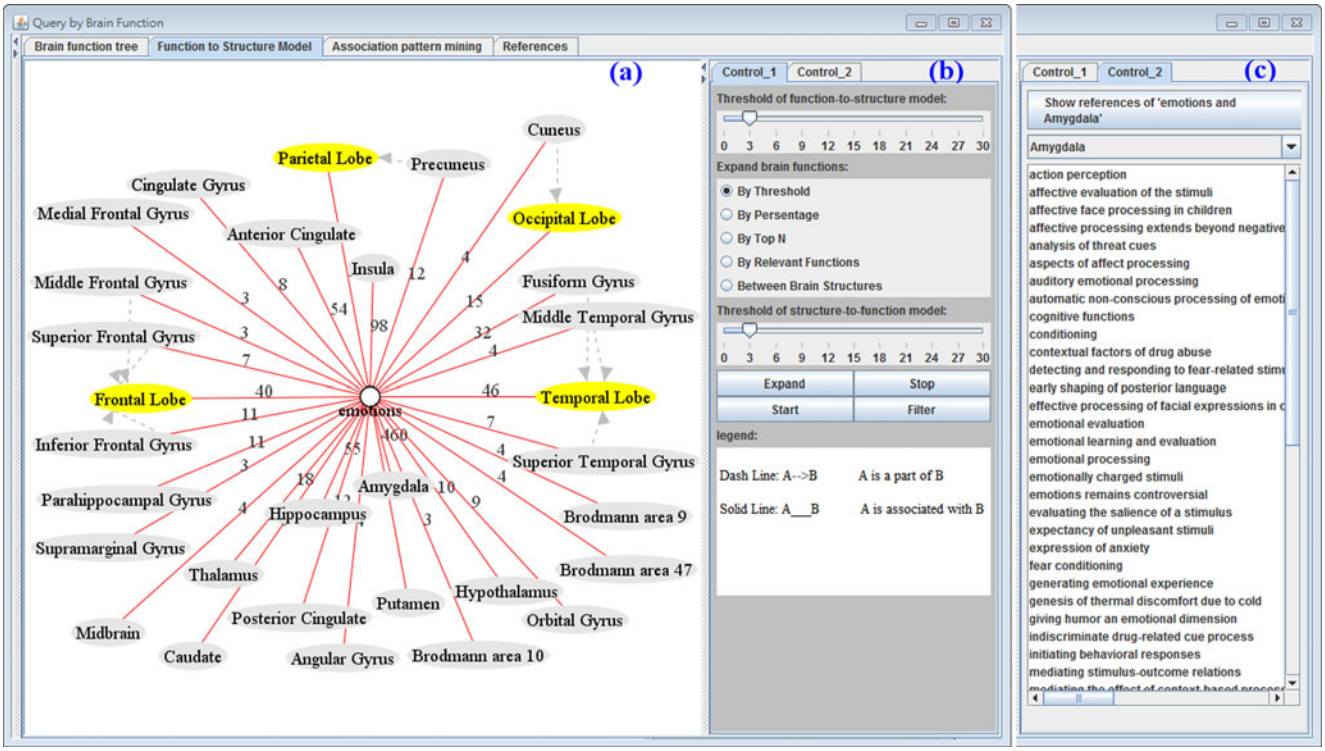


Fig. 4 Screenshot showing the window for manipulating the function-to-structure co-occurrence model: **a** the model for the emotion function. The co-occurrence frequencies shown on the lines indicate the numbers of sentences in which the brain function and brain structure co-occur in the same sentence. The gray arrow lines between the two anatomical nodes indicate the "is_a_part_of" relationship, and the nodes they point to are the parent nodes; **b** the control panel, used to set co-occurrence parameters; **c** the roles of the selected brain structure are listed in this tab

term as defined by the terminologies of UMLS. The function-to-structure co-occurrence model (Fig. 4) visualizes the relationship between brain structures and the queried brain function. The central node is the queried term, and other nodes represent the relevant brain structures. The co-occurrence frequencies of brain structures and the queried function in a sentence are noted on a link. Moreover, the BrainKnowledge also provides the relationships among brain structures as dashed arrow lines. The arrow head denotes the parent mode in an "is_a_part_of" relationship, as defined by either the Talairach Daemon database (Lancaster et al. 2000) or NeuroNames (Bowden and Dubach 2003). BrainKnowledge allows users to set the minimum threshold of co-occurrence models in order to filter out function nodes with low co-occurrence frequencies, which might be caused by chance. In addition, users can expand the node for each brain structure to reveal more brain functions that may also be relevant to this particular brain structure. This should assist users in finding connections between these structures and the queried function. Furthermore, users are also able to show more brain functions in these structures related to the queried function, to help further understand the relationships between brain structures and the queried function. Figure 4 shows an example of manipulating the function-to-structure co-occurrence model for emotion. We retrieve the brain structures with the co-occurrence frequency ≥ 3 by setting the threshold of function-to-structure model in the control panel. The brain structure relevant to emotion with the highest co-occurrence frequency is the amygdala. The user can then select "amygdala" from the brain structure list in the control panel 2 to view the roles of the amygdala extracted by BrainKnowledge from the collected literature. If a user is interested in retrieving more information about emotion or a particular function-to-structure link, they can read the relevant indexed sentences directly from the original MEDLINE abstracts, or even access the full-text papers via hypertext links. Figure 5 shows an example of the references that are relevant to emotion function. The references are listed by brain structure(s), brain function(s), first author, year of publication, co-occurrence sentence, and journal name. The brain structures and brain functions are extracted from the sentences by BrainKnowledge. The information helps scientists get digest information quickly instead of having to read the sentence or the entire abstract.

Query by Brain Structure

BrainKnowledge allows users to explore relevant information, such as the location, the function, and the brain

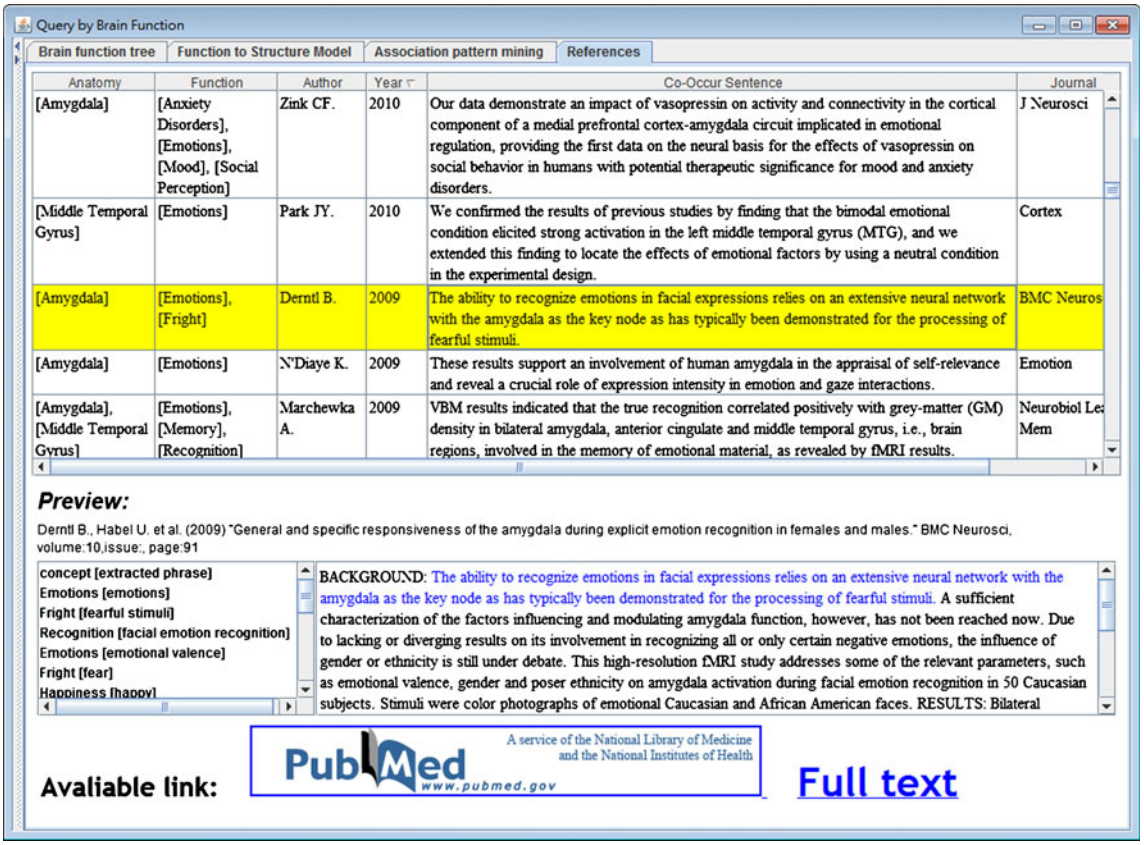


Fig. 5 Screenshot of the references panel. In this case, we show the sentences that describe the queried function (here, the emotion function). The top panel shows the retrieved brain structures, functions, and relevant sentences, and the detailed abstract is shown in the bottom panel. BrainKnowledge highlights retrieved brain structures and functions that might capture the interest of the user

structure co-occurrence model of a designated brain structure. The query is performed by either (1) selecting an item from a list of brain structure names, (2) keying in the stereotaxic Montreal Neurological Institute (MNI) (Evans et al. 1993) or Talairach (Talairach and Tournoux 1988) coordinates, or (3) clicking on a specific location in the three-view 2D MRI images of a standard brain with the mouse. Figure 6 shows an example of querying by selecting the amygdala from the brain structure name list. When a user chooses a brain structure name from the brain structure name list, BrainKnowledge will highlight the selected structure in the three-view 2D MRI images and shows the location and shape of the queried structure. In addition, BrainKnowledge will automatically show the top five functions of the structure-to-function co-occurrence model for the selected brain structure. The structure-to-function co-occurrence model provides information about the functions that are relevant to the queried brain structure gathered from the database. Moving the cursor onto the function nodes of the structure-to-function model will display the definition(s) defined by the terminologies in UMLS. This display helps users better understand the brain functions of the queried brain structure. In addition, users can manipulate the interactive structure-to-function model by accessing the "Structure-to-Function Model" tab, with manipulative procedures similar to those in the function-to-structure model.

BrainKnowledge also automatically extracts roles of the queried brain structure from the collected literature as described in *The Named Entity Extraction Module.* The retrieved results can be accessed from the "Roles of the Brain Structure" tab. They are listed by first author, year of publication, summary, and journal name. This can help scientists understand the opinions of other neuroscientists on the roles of specific brain structures.

In order to understand possible associations between brain structures, BrainKnowledge provides a brain structure co-occurrence model between different brain structures. In this model, BrainKnowledge retrieves all brain structures that co-occur within the queried brain structure in the literature. It also provides brain functions if the two brain structures also co-occur within a brain function term in the sentence. This can help scientists understand which brain functions contribute to the link. For instance, the amygdala has strong associations with the hippocampus and they are frequently mentioned in the literature with the emotion and memory process.

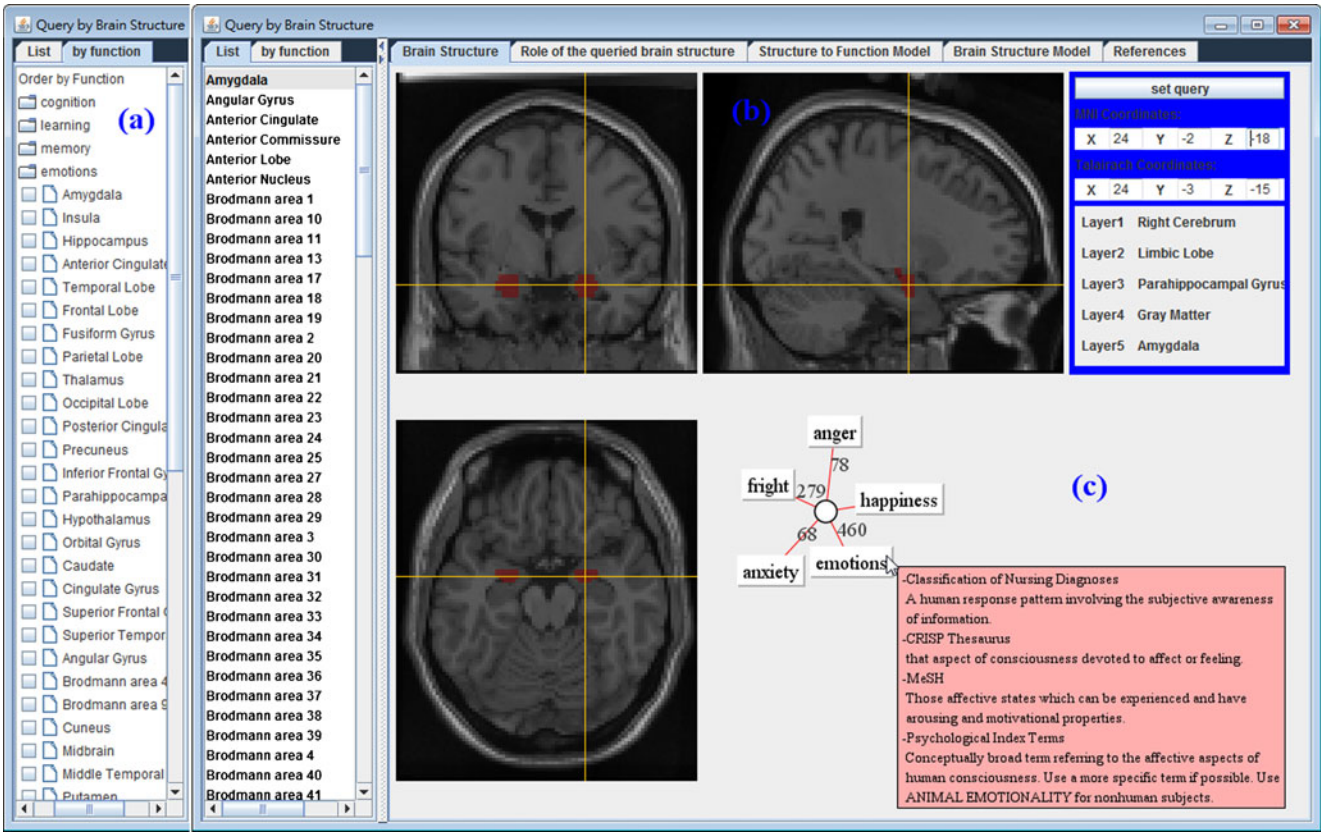


Fig. 6 Screenshot showing the window for querying by brain structure. This interface includes 5 tabs that show the brain structure, the roles of the brain structure, the structure-to-function model, the brain structure model, and references. Here we perform the query by selecting "amygdala" from the left panel. **a** Brain structural names are listed in alphabetical order or categorized by function; **b** Three-view 2D MRI images are used to show both the location and shape of the queried brain structure. **c** The top five functions of the structure-to-function model of the queried brain structure. Moving the cursor over any term will display definition(s) as defined by the terminologies of UMLS

The same brain structure co-occurrence model can also be applied to two-queried brain structures. In the two-queried brain structures model, if a brain area co-occurs within both the two queried brain structures in the same sentence, we color this brain area yellow. It means these three brain structures are directly related. On the other hand, if a brain area co-occurs with the two queried brain structures one at a time, or co-occurs with only one of the two queried brain structures, this area bridges an indirect relationship between the two queried brain structures. We color this brain area white. An example of a brain structure co-occurrence model for the amygdala and hippocampus is shown in the *An Application Example: Studies of Affect* section.

Integrating fMRI Experimental Data with the Literature Results

The most important function in BrainKnowledge is to integrate the fMRI experimental data with the extracted literature results. In BrainKnowledge, we provide two subsystems to integrate fMRI data with information extracted from the literature. The first subsystem compares the fMRI experimental data with the mined-literature results (Fig. 7). The second uses the information extracted from the literature to help neuroscientists understand the experimental results (Fig. 8). SPM is a widely used tool for analyzing experimental fMRI data. However, SPM provides analysis results in the form of stereotaxic coordinates. It is difficult for users to obtain the brain structure name from the coordinates. Researchers get this information by other tools, such as xjview (http://www.alivelearn.net/xjview/). Hence, BrainKnowledge presents users with a friendly interface to import a SPM_T file, which stores the t-test result of a particular contrast, and then obtains the brain structure name of the activation area and relevant information extracted from the literature.

In order to compare the SPM statistics with the brain structures extracted from the literature, users must first select a brain function of interest from our brain function tree. BrainKnowledge then processes the SPM statistical files to get the coordinates of the activated area; that is, the voxels with T-statistics greater than a user-defined threshold. For retrieving knowledge from the literature, the 3D coordinates given by SPM were converted from those of the MNI to Talairach using the algorithm provided by Brett et al. (2001) and Lancaster et

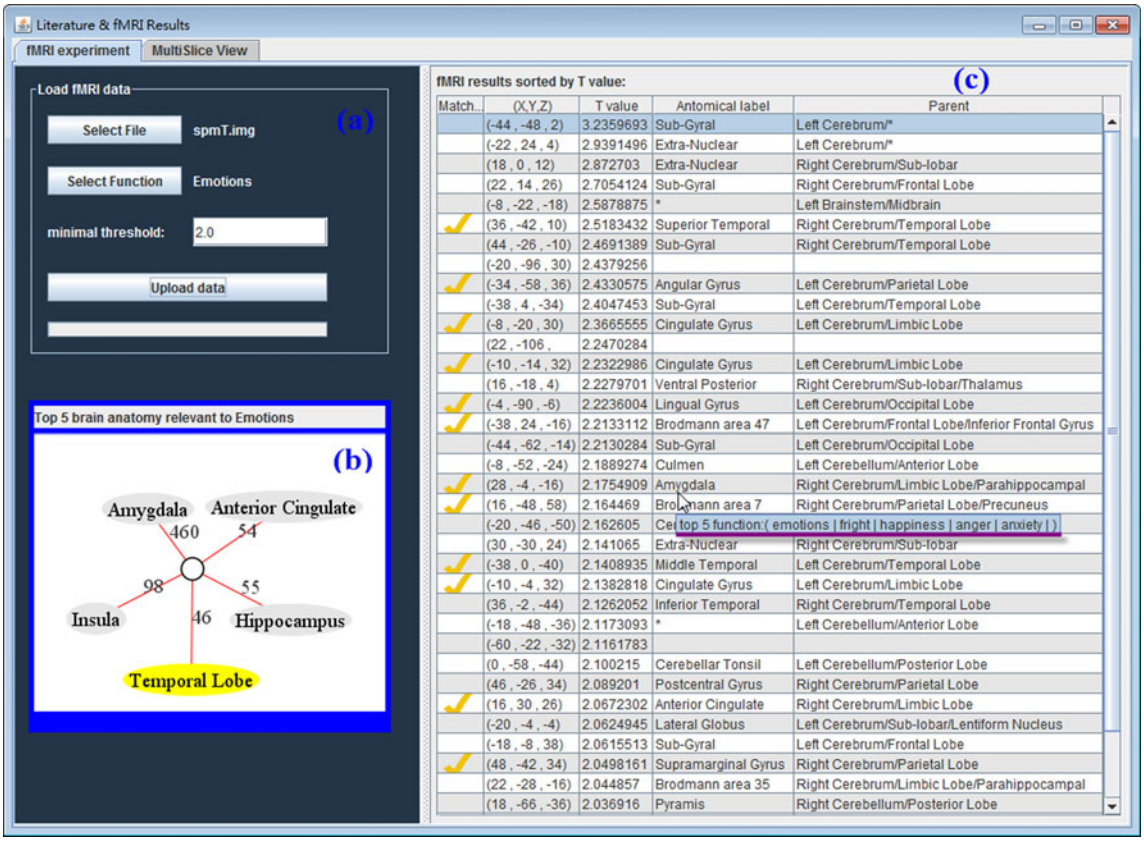


Fig. 7 Screenshot showing the window for integrating fMRI experimental data with the literature results. **a** fMRI experimental result upload panel; **b** Top 5 brain structures relevant to the interested function (here with the emotion function); **c** fMRI results sorted by T-values. The yellow checks in the list means these brain structures are relevant to the function of interest in the literature. Moving the cursor onto the brain structure name will display the top five relevant functions retrieved from our structure-to-function model

al. (2007). In addition, BrainKnowledge retrieves the Talairach labels gathered from both the activation coordinates and also from the function-to-structure co-occurrence model of the interested function. BrainKnowledge then provides a list that shows the matched brain structures between the experimental results and the literature. Moreover, moving the cursor onto the brain structure will display the top five relevant functions retrieved from our structure-to-function co-occurrence model. This can help neuroscientists become aware of possible new findings and/or discrepancies in their results.

With the second subsystem, BrainKnowledge overlays the activation map on an MRI template and visualizes the result in a multiple-slice view. Users can then simply click on the activation coordinates to retrieve the selected region's structural name and the information related to the activated area, such as MNI and Talairach coordinates, roles of the activated area, the top five functions of the activated area, and the top five functions of the activated area conditioned by the function of interest. If users want to learn more about any specific brain structure, they can click on the "More" button to access the query by brain structure discussed above. All of this information is automatically extracted from the literature by our literature extraction and mining module. Using the information extracted from the literature should help neuroscientists interpret and support the results of their experiments.

An Application Example: Studies of Affect

In our literature database, there are 2,224 sentences (20% of the indexed brain functions in our database) related to emotion and the related brain structures. Among the 2,224 sentences, 241 sentences were retrieved by direct references to the keyword "emotion," 560 sentences were retrieved by using the brain function dictionary to extend it to synonymous terms and morphological features, and 1423 sentences referred to the child concepts of emotion. BrainKnowledge provides a broader concept-based query as well as a wider range of data than a normal keyword-based search.

Table 1 presents the experimental tasks and the top 3 brain structures retrieved by BrainKnowledge as being relevant to emotion and its four child concepts: pain, fright, happiness, and anger. Their function-to-structure co-

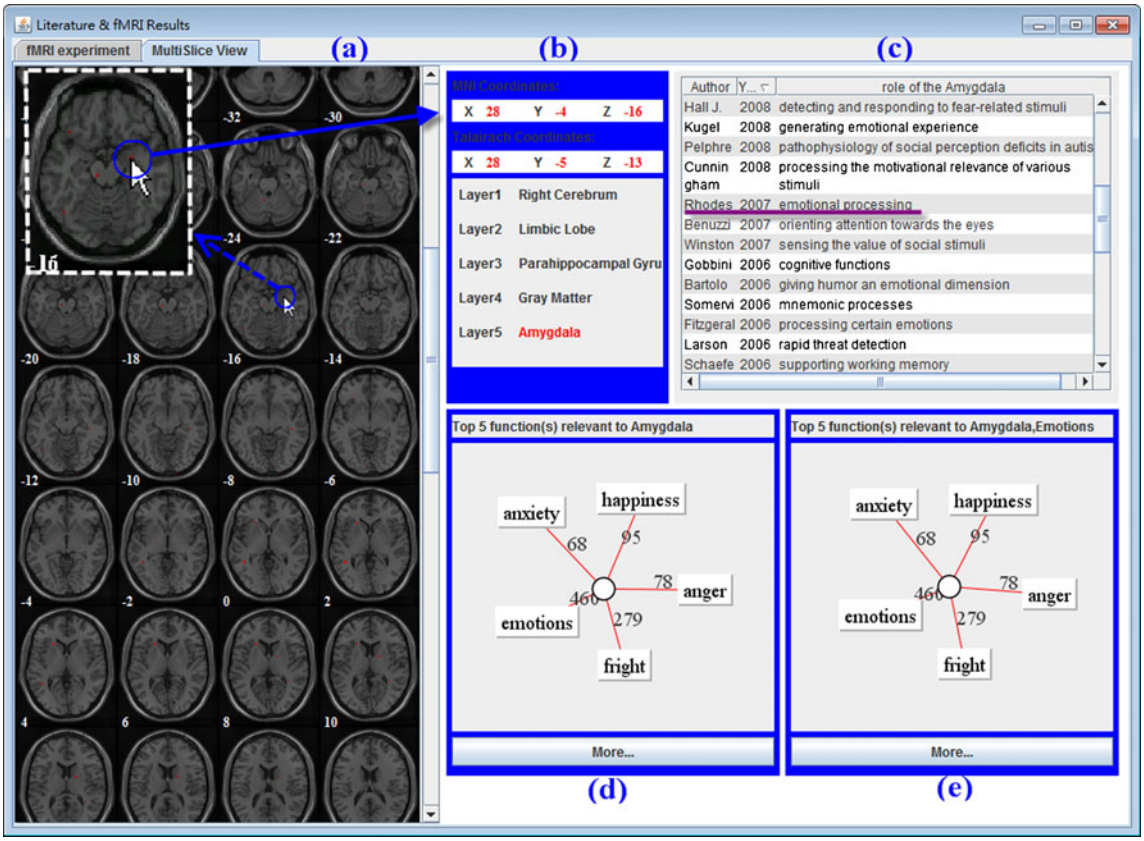


Fig. 8 Screenshot showing the window for visualizing the activation data in multiple-slice view and using the information extracted from the literature to help neuroscientists understand the experimental results. The cursor is clicked on the slice −16 mm at the coordinates (28,-4,-16) and the position is the amygdala. **a** The multiple-slice view; **b** Information about the coordinates and brain structure name; **c** Roles of the activated area (here with the amygdala); **d** Top 5 functions of the activated area; **e** Top 5 functions of the activated area conditioned by the interested function (here with the emotion function)

Table 1 The experimental tasks and brain structures relevant to emotion and its four child concepts: pain, fright, happiness, and anger

Concept	Relevant experimental task(s)	Top 3 relevant brain structures
Emotion	Affective priming task, Attention-demanding task, Breath-focused attention task, Conscious spatial monitoring task, Decreased emotional task, Digit-sorting task, Emotional Congruence task, Emotion Stroop task, Emotion face assessment task, Emotion labeling task, Emotional processing task, Emotional decision task, Emotional faces encoding task, Emotional face-matching task, Emotional pictures task, Emotional stress task, Emotional valence Stroop task, Explicit emotion recognition task, General word task, Geometric shapes task, Immediate recognition memory test, Labeling task, Letter task, Memory task, Negative emotional faces task, Passive visual task, Perceptual matching task, Visuospatial processing task, Working memory task	Amygdala, Insula, Hippocampus
Pain	Attention-demanding task, Counting task, Imagination task, Painful thermal task, Pressure pain test, Sensory delayed-discrimination task	Insula, Thalamus, Anterior Cingulate
Fright	Roland's Hometown Walking Task, Dot-probe task, Fearful face task, Geometric shapes task, Negative emotional faces task, Perceptual matching task, Response inhibition task, Subsequent memory test	Amygdala, Fusiform Gyrus, Hippocampus
Happiness	Emotion processing task, Face-in-the-crowd task, Visuospatial processing task	Amygdala, Hippocampus, Anterior Cingulate
Anger	Face-in-the-crowd task, Geometric shapes task, Implicit task, Negative emotional faces task, Perceptual matching task	Amygdala, Insula, Hippocampus

occurrence models are shown in panels (a) to (d), respectively, of Fig. 9. From Table 1, we notice that the amygdala and hippocampus are all highly relevant to emotion, fright, happiness, and anger, but not pain. Instead, the amygdala and hippocampus are only the 4th and the 6th brain structures, respectively, most relevant to pain (see Fig. 9(b) function-to structure co-occurrence model of pain). The top 3 most relevant brain structures concerning pain in the

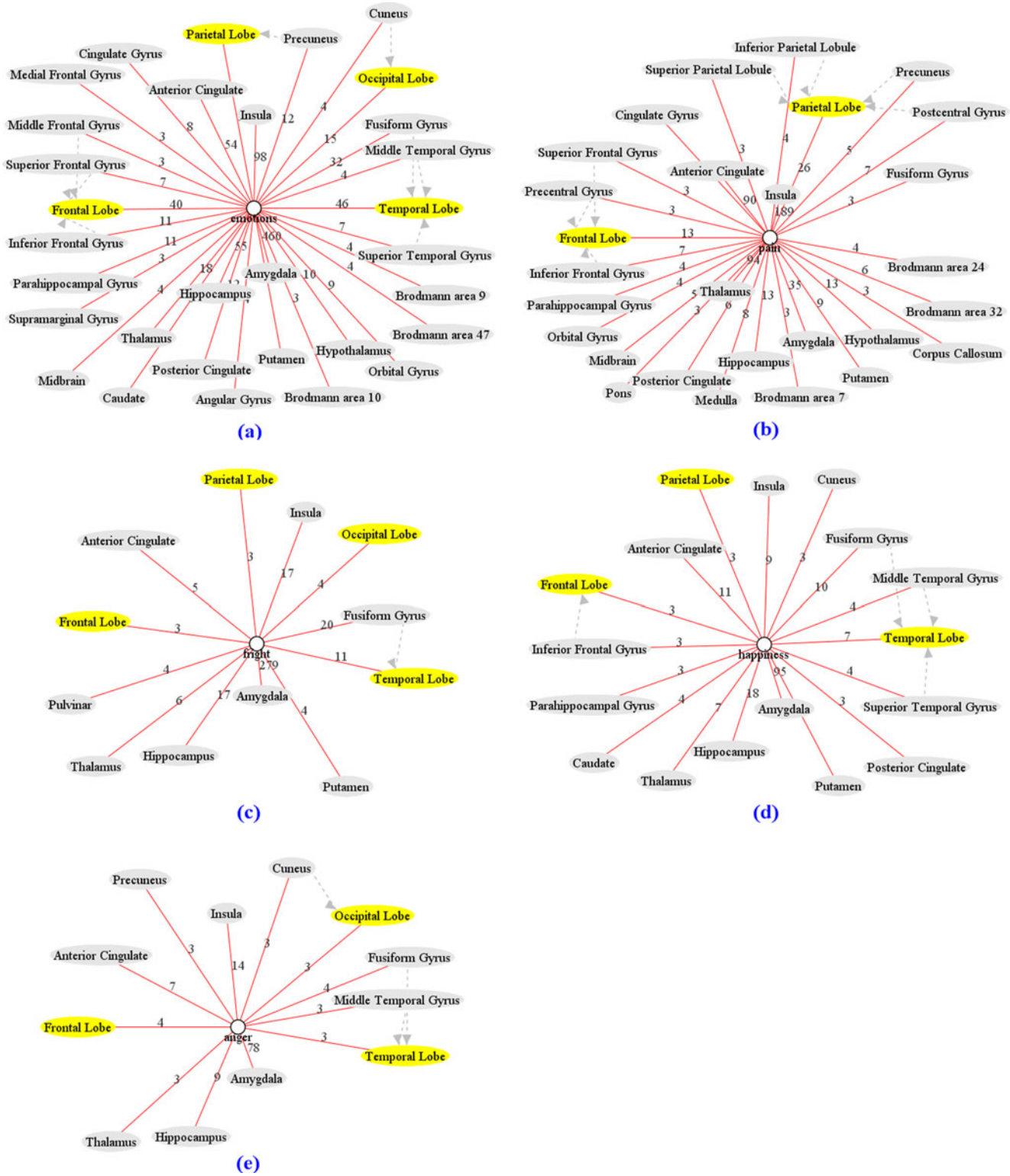


Fig. 9 The function-to-structure co-occurrence models of emotion and its four child concepts. The model for **a** emotion; **b** pain; **c** fright; **d** happiness; **e** anger

literature are the insula, thalamus, and anterior cingulate. These associations are consistent with the fMRI experiments that show the insula, thalamus, and anterior cingulate are all important to pain and other basic emotions (Botvinick et al. 2005; Maihofner et al. 2005; Williams et al. 2007; Raij et al. 2009; Pogatzki-Zahn et al. 2010). Moreover, the thalamus plays an important role in relaying and integrating sensory information (Portas et al. 1998). From the function-to-structure co-occurrence model of pain, we know that pain is associated not only with emotion but also sensation or perception. Notice that, most publicly available vocabulary sources have no link between "emotion" and "pain." Nevertheless, we were able to use UMLS to reconstruct this link in the literature. Thus, using the retrieved brain structures relevant to its function might help us validate the soundness of our brain function tree.

In Fig. 9(a), the function-to-structure co-occurrence model for emotion showed a clear and strong relationship between emotion and the amygdala, the insula, and the hippocampus. This is consistent with previous empirical reports (Adolphs et al. 1994; Whalen et al. 1998; Phan et al. 2002; Wright et al. 2002). Furthermore, we applied the association mining algorithm as described in *Knowledge Representation* to discover brain structure patterns from the emotion dataset. As shown in Fig. 10, with 3% minimum support, the amygdala and the insula, and the amygdala and the hippocampus were two frequent association patterns likely to co-occur with emotion. The amygdala and the hippocampus had an association not only with emotion in general, but also with fright and happiness in particular. In addition, they also associated with other functions, such as memory. This result may imply a functional association between the amygdala and the hippocampus as well. We then applied these two brain structures to a brain structure co-occurrence model (Fig. 11), which shows the association between brain structures. As shown in Fig. 11, many brain structures, such as the insula and the thalamus (yellow nodes) have direct relationships to both the amygdala and the hippocampus. It is known that the insula, amygdala, and hippocampus co-occur in both emotion and pain. The brain structure co-occurrence model might, therefore, have an implication in the brain connectivity model.

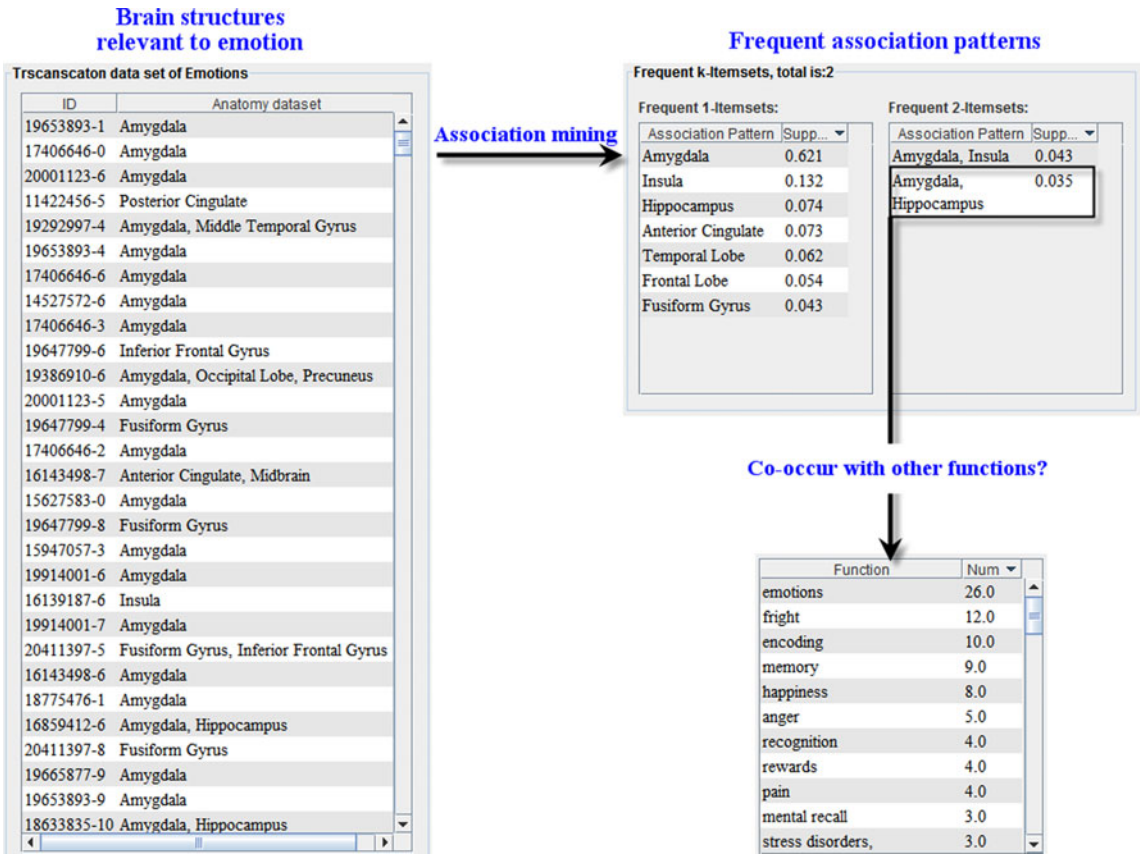


Fig. 10 The process of discovering brain structure patterns from the emotion dataset. The left panel is the dataset of the studies of affect. After applying the association mining algorithm, the association patterns are shown in the top right panel. Furthermore, we can retrieve more functions that are relevant to the selected association pattern, as shown in the bottom right panel. From this case, the amygdala and hippocampus are the frequent association pattern in the studies of affect and this pattern also co-occurs in other functions such as memory

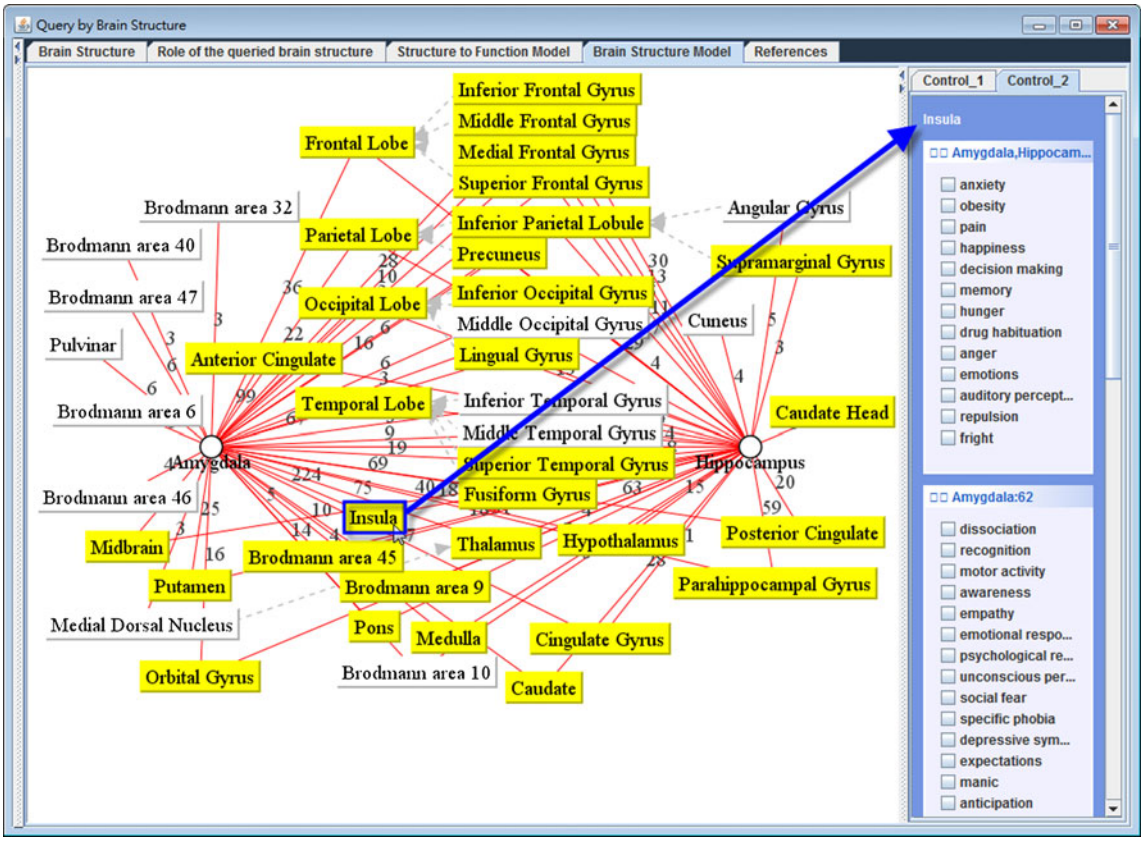
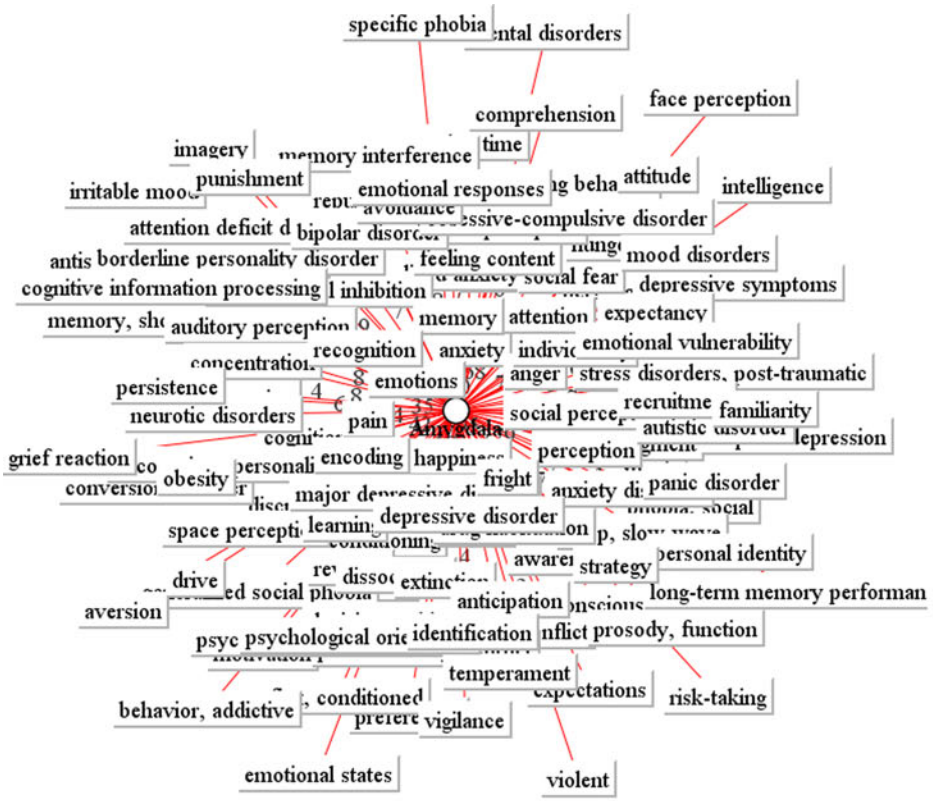


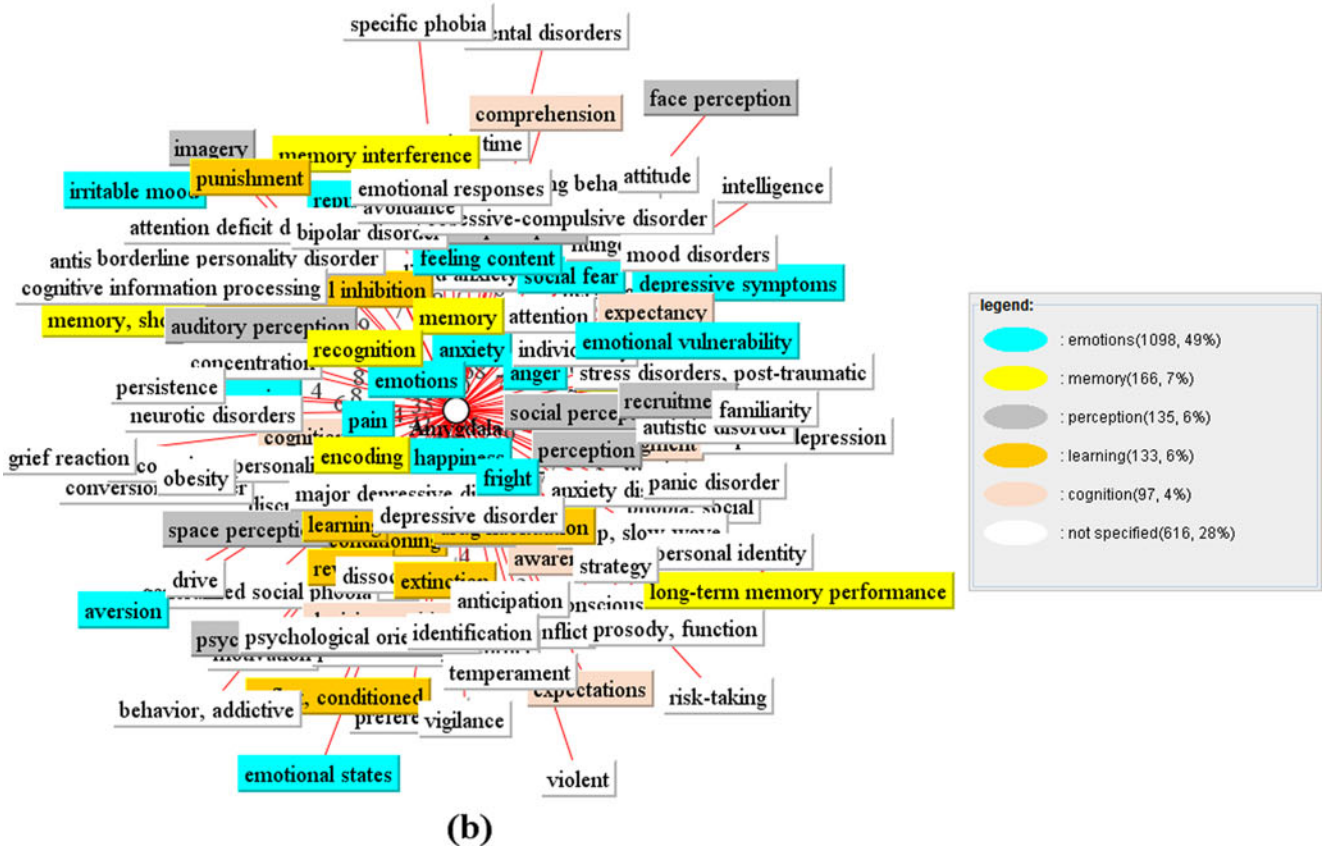
Fig. 11 Brain structure co-occurrence model of the amygdala and hippocampus. We can see that the insula has a direct relation to both the amygdala and hippocampus. Here we click on the node "Insula" to show the brain functions between the insula, amygdala, and hippocampus, the functions between the insula and amygdala, and the functions between the insula and hippocampus (shown in the right panel)

We then used a real experiment dataset to illustrate the ability of BrainKnowledge to integrate the fMRI experimental data and the literature mining results. This dataset was from Simpson et al. (2000), who studied BOLD activation to emotional response to negatively valenced and neutral pictorial stimuli. It was downloaded from the Functional Magnetic Resonance Imaging Data Center (fMRIDC; http://www.fmridc.org) (Van Horn et al. 2001). We reanalyzed the data with motion correction, normalization, and smoothing with SPM using default parameters. The statistical analysis used a general linear model with the designed matrix constructed from the instructions provided by the original authors. We then uploaded the SPM statistical file, shown in Fig. 7(a), into BrainKnowledge and chose "emotion" as the function of interest. The system displayed the top 5 most relevant brain structures to the function of interest (Fig. 7(b)). Figure 7(c) shows a list of the activation from the input data. Areas such as the superior temporal lobe, the cingulate gyrus, and the amygdala also appeared in the function-to-structure co-occurrence model of emotion function were marked by the system. That is, these structures were frequently reported in the previous studies as involved in affect processing. The brain structures, such as cingulate gyrus, with a tick mark in panel (c) but not in panel (b), are those that have a co-occurrence with emotion but did not make the top 5 list. The data can be visualized in a multiple-slice view (Fig. 8). Clicking on an activated area (such as the amygdala at coordinates (28,-4,-16)) would reveal the relevant information extracted by BrainKnowledge. This may help users know what other neuroscientists think about the selected area. We then selected the amygdala for a brain function query and retrieved the structure-to-function co-occurrence model for the amygdala (Fig. 12(a)). Using our hierarchical concept-based brain function dictionary, we were able to show that the amygdala is critical to emotion-related processing (Fig. 12(b)). This result is consistent with neurobiological studies (Adolphs et al. 1994, Whalen et

Fig. 12 The structure-to-function co-occurrence model for the amygdala. **a** The model with co-occurrence frequency ≥ 3; **b** The classifying function by hierarchical brain function tree. The legend shows the color of high-order concepts in brain function order in terms of the sum of co-occurrence frequencies of the child nodes. Here we were able to show that the amygdala is critical to emotion-related processing ▶


specific phobia
comprehension
face perception
imagery
memory interference
time
punishment
attitude
intelligence
emotional responses
irritable mood
attention deficit d
bipolar disorder
antis borderline personality disorder
feeling content
mood disorders
cognitive information processing
depressive symptoms
memory, sh
auditory perception
memory
attention
expectancy
recognition
anxiety
emotional vulnerability
persistence
emotions
anger
stress disorders, post-traumatic
neurotic disorders
pain
recruitme
familiarity
grief reaction
encoding
perception
obesity
fright
panic disorder
major depressive
depressive disorder
space percepti
learnin
awarei
strategy
personal identity
drive
anticipation
long-term memory performan
aversion
psyc psychological orie
identification
nflict prosody, function
temperament
behavior, addictive
conditioned
vigilance
risk-taking
emotional states
violent

(a)


specific phobia
comprehension
face perception
imagery
memory interference
time
punishment
attitude
intelligence
emotional responses
irritable mood
attention deficit d
bipolar disorder
antis borderline personality disorder
feeling content
mood disorders
cognitive information processing
depressive symptoms
memory, sh
auditory perception
memory
attention
expectancy
recognition
anxiety
emotional vulnerability
persistence
emotions
anger
stress disorders, post-traumatic
neurotic disorders
pain
recruitme
familiarity
grief reaction
encoding
perception
obesity
fright
panic disorder
depressive disorder
space percepti
learnin
awarei
strategy
personal identity
drive
anticipation
long-term memory performance
aversion
psyc psychological orie
identification
nflict prosody, function
temperament
behavior, addictive
conditioned
vigilance
risk-taking
emotional states
violent
legend:
: emotions(1098, 49%)
: memory(166, 7%)
: perception(135, 6%)
: learning(133, 6%)
: cognition(97, 4%)
: not specified(616, 28%)

(b)

al. 1998; Sergerie et al. 2008; Rhodes et al. 2007). For instance, the user can see the quote "emotional processing" from the query (see Fig. 8(c) for the roles of the amygdala). If users are interested in retrieving more information regarding a certain function or a brain structure, they can read the relevant indexed sentences directly from the original MEDLINE abstracts or even access the full-text papers via hypertext links (Fig. 5). The purpose of referring to the original sentence and abstract is to minimize misinterpretations.

Discussion and Conclusion

There is a critical need for information extraction and organization from the fMRI literature to help neuroscientists explain and support their findings from their fMRI experimental results. We have therefore provided a system (BrainKnowledge) that automatically downloads and extracts information from the literature in order to generate brain-function co-occurrence models and discover brain structure association patterns. The extracted information and co-occurrence models are then used to support and interpret fMRI experimental results, thereby helping neuroscientists become aware of possible new findings and/or discrepancies in their results.

The core of BrainKnowledge is based on the literature extraction and mining module (Hsiao et al. 2009). To the best of our knowledge, there is currently no adequately comprehensive resource for brain function vocabulary that is appropriate for named entity extraction. Therefore, we construct a generalized hierarchical concept-based dictionary of brain functions to serve as our dictionary (Hsiao et al. 2009). This dictionary merged 23 vocabulary sources, such as MeSH, Psychological Index Terms, and similar resources, to yield a broader coverage. We then used the UMLS semantic type to filter out terms in these various vocabulary sources that are irrelevant to brain functions. Experts in neuroscience were involved in deciding which semantics or concepts were not appropriate for our purpose during the dictionary construction process. Such a method allows us to construct a fairly accurate dictionary (Hsiao et al. 2009). In addition, using the hierarchical concept-based dictionary of brain functions to extend the queried function terms provides a broader concept-based query as well as a wider range of data than a normal keyword-based search. Moreover, using our hierarchical concept-based brain function dictionary to classify the functions in structure-to-function co-occurrence models can allow us to study brain functions in a broader, more holistic way.

In the term-mapping evaluation experiment reported in our previous study (Hsiao et al. 2009), each expert took about 5 h to complete the assignment. This result illustrates how time-consuming and tedious the whole named entity extraction process can be for human experts. BrainKnowledge can help experts annotate a large number of terms (such as brain functions, brain structures, and experimental tasks) and organize information extracted from different literature to form the brain-function co-occurrence models in a very short period of time, thus saving scientists valuable time previously wasted by sorting through all of the raw data by themselves.

The meta-analysis tools, such as BrainMap, SumsDB, AMAT, and the Brede database, provide coordinates for performing meta-analytic research. However, the coordinates are currently entered by human beings. In BrainKnowledge, we extract information from PubMed MEDLINE abstracts, which contain, presumably, the most essential information in the paper. However, findings in scientific abstracts are almost always presented by brain name instead of coordinates, although coordinates do appear in the full text. Thus, BrainKnowledge only extracts brain names rather than coordinates. We do acknowledge that abstracts contain only a summary and, thus, a subset of the total information in a paper. The current trend is moving towards parsing information from the full text literature. In the future, we plan to extend BrainKnowledge's capability to include the full text scale in order to gather more information, although there are still many difficulties that must be overcome, such as that available papers are not always in the same file format (i.e., pdf, html, etc.) nor the same organization or style (e.g. the introduction-method-results-discussion, or IMRAD, structure vs. the introduction-result & discussion-method structure). Future developments will also be directed towards further expanding our named entity extraction algorithm to include more categories beyond the three currently used in this study (brain structures, brain functions and experimental tasks). Such an expansion could help augment the meta-analysis of published material and in turn greatly benefit experts in this field.

The assumption of co-occurrence model is based on whether or not brain structures and functions are mentioned together in MEDLINE sentences. When the two frequently appear together, it implies that there might be an underlying biological relationship between them. Co-occurrence frequencies, shown on the lines between the terms in the co-occurrence model, indicate the numbers of sentences in which the two entities co-occur in a sentence. However, the order of the frequency in the co-occurrence model does not necessarily equate to the sequence of brain mechanisms. In other words, the frequencies in the structure-to-function co-occurrence model may not describe the range of importance or the sequence of the functions contributed by the queried brain structure. Identifying the underlying relationships such as these will require more work in the future (for example, further text mining work or more fMRI experiments to examine the relationship should be carried out).

In summary, we have presented herein a human brain function mapping knowledge-base (BrainKnowledge) system, which combines fMRI datasets with the published literature in a comprehensive framework for studying human brain activities. BrainKnowledge provides three major system features: (1) it allows users to utilize the brain function tree to search for brain activation models; (2) it performs queries by brain structures; and (3) it compares the fMRI data with data extracted from the literature. Presently, BrainKnowledge provides three co-occurrence models that allow users to view associations between the brain and functions in a visual map. Each model has been generated from a vast amount of extracted Medline abstracts. In addition, we utilized the association mining algorithm to discover interesting patterns from the extracted data. In this study, we have demonstrated the capabilities of BrainKnowledge and have provided an example with the studies of affect. The integration of the extracted literature information into fMRI datasets may be helpful in supporting neuroscientists' research and comparing experimental results from different studies.

Information Sharing Statement

The software described in this paper can be obtained by contacting the author, or at http://BrainKnowledge.ee.ntu.edu.tw. Requests for the software should include name, institution and e-mail. The project is still in its preliminary stages. We would greatly appreciate any comments that can help us improve future releases of BrainKnowledge through e-mails or comments left on the BrainKnowledge Web site.

Acknowledgements We would like to thank Dr. Chung-Ming Chen, Dr. Der-Yow Chen, Dr. Hsin-Hsi Chen and Dr. Keng-Chen Liang for their helpful discussions in this work. This research was partially supported by grants from National Science Council (Taiwan) NSC97-2321-B-002-044 and NSC98-2627-B-002-014 to CCH and NSC97-2410-H-002-158-MY2 to CCC. The data reported in this paper was from the fMRI Data Center archive (www.fmridc.org, accession number 2-2000-1119F).

References

Adolphs, R., Tranel, D., Damasio, H., & Damasio, A. (1994). Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Nature, 372*, 669–672.

Agrawal, R., & Srikant, R. (1994). Fast algorithms for mining association rules. Paper presented at the 20th Int. Conf. on Very Large Data Bases, 487–499, 1994.

Barinaga, M. (2003). Neuroimaging. Still debated, brain image archives are catching on. *Science, 300*, 43–45.

Botvinick, M., Jha, A. P., Bylsma, L. M., Fabian, S. A., Solomon, P. E., & Prkachin, K. M. (2005). Viewing facial expressions of pain engages cortical areas involved in the direct experience of pain. *Neuroimage, 25*, 312–319.

Bowden, D. M., & Dubach, M. F. (2003). NeuroNames 2002. *Neuroinformatics, 1*, 43–59.

Brett, M., Christoff, K., Cusack, R., & Lancaster, J. (2001). Using the Talairach atlas with the MNI template. *Neuroimage, 13*, 85.

Evans, A. C., Collins, D. L., Mills, S. R., Brown, E. D., Kelly, R. L., & Peters, T. M. (1993). 3D statistical neuroanatomical models from 305 MRI volumes. Paper presented at the IEEE Nucl. Sci. Symp. Med. Imaging Conf., 1813–1817, Piscataway, NJ, 1993.

Friston, K. J., Jezzard, P., & Turner, R. (1994). Analysis of functional MRI time-series. *Human Brain Mapping, 1*, 153–171.

Hsiao, M. Y., Huang, W. J., Chen, D. Y., & Chen, J. H. (2007). The human brain functional mapping knowledge base with 3D visualization. Presented at the 13th Annual Meeting of the Organization for Human Brain Mapping, June 10–14, 2007, Chicago, IL.

Hsiao, M. Y., Chen, C. C., & Chen, J. H. (2009). Using UMLS to construct a generalized hierarchical concept-based dictionary of brain functions for information extraction from the fMRI literature. *Journal of Biomedical Informatics, 42*, 912–922.

Jelier, R., Jenster, G., Dorssers, L. C., van der Eijk, C. C., van Mulligen, E. M., Mons, B., et al. (2005). Co-occurrence based meta-analysis of scientific texts: retrieving biological relationships between genes. *Bioinformatics, 21*, 2049–2058.

Jenssen, T. K., Laegreid, A., Komorowski, J., & Hovig, E. (2001). A literature network of human genes for high-throughput analysis of gene expression. *Nature Genetics, 28*, 21–28.

Laird, A. R., Lancaster, J. L., & Fox, P. T. (2005). BrainMap: the social evolution of a human brain mapping database. *Neuroinformatics, 3*, 65–78.

Lancaster, J. L., Woldorff, M. G., Parsons, L. M., Liotti, M., Freitas, C. S., Rainey, L., et al. (2000). Automated Talairach atlas labels for functional brain mapping. *Human Brain Mapping, 10*, 120–131.

Lancaster, J. L., Tordesillas-Gutierrez, D., Martinez, M., Salinas, F., Evans, A., Zilles, K., et al. (2007). Bias between MNI and Talairach coordinates analyzed using the ICBM-152 brain template. *Human Brain Mapping, 28*, 1194–1205.

Li, X., Cai, H., Xu, J., Ying, S., & Zhang, Y. (2010). A mouse protein interactome through combined literature mining with multiple sources of interaction evidence. *Amino Acids, 38*, 1237–1252.

Maihofner, C., Forster, C., Birklein, F., Neundorfer, B., & Handwerker, H. O. (2005). Brain processing during mechanical hyperalgesia in complex regional pain syndrome: a functional MRI study. *Pain, 114*, 93–103.

Muller, H., & Mancuso, F. (2008). Identification and analysis of co-occurrence networks with NetCutter. *PLoS ONE, 3*, e3178.

Nielsen, F. A. (2003). The Brede database: a small database for functional neuroimaging. NeuroImage, 19, Presented at the 9th International Conference on Functional Mapping of the Human Brain, e1788–e1789, June 19–22, 2003, New York.

Nielsen, F. A., Hansen, L. K., & Balslev, D. (2004). Mining for associations between text and brain activation in a functional neuroimaging database. *Neuroinformatics, 2*, 369–380.

Nielsen, F. A., Christensen, M. S., Madsen, K. H., Lund, T. E., & Hansen, L. K. (2006). fMRI neuroinformatics. *IEEE Engineering in Medicine and Biology Magazine, 25*, 112–119.

Ogawa, S., Tank, D. W., Menon, R., Ellermann, J. M., Kim, S. G., Merkle, H., et al. (1992). Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. *Proceedings of the National Academy of Sciences of the United States of America, 89*, 5951–5955.

Phan, K. L., Wager, T., Taylor, S. F., & Liberzon, I. (2002). Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage, 16*, 331–348.

Pogatzki-Zahn, E. M., Wagner, C., Meinhardt-Renner, A., Burgmer, M., Beste, C., Zahn, P. K., et al. (2010). Coding of incisional pain in the brain: a functional magnetic resonance imaging study in human volunteers. *Anesthesiology, 112*, 406–417.

Portas, C., Goldstein, J., Shenton, M., Hokama, H., Wible, C., Fischer, I., et al. (1998). Volumetric evaluation of the thalamus in schizophrenic male patients using magnetic resonance imaging. *Biological Psychiatry, 43*, 649–659.

Raij, T. T., Numminen, J., Narvanen, S., Hiltunen, J., & Hari, R. (2009). Strength of prefrontal activation predicts intensity of suggestion-induced pain. *Human Brain Mapping, 30*, 2890–2897.

Ramani, A. K., Bunescu, R. C., Mooney, R. J., & Marcotte, E. M. (2005). Consolidating the set of known human protein-protein interactions in preparation for large-scale mapping of the human interactome. *Genome Biology, 6*, R40.

Rhodes, R. A., Murthy, N. V., Dresner, M. A., Selvaraj, S., Stavrakakis, N., Babar, S., et al. (2007). Human 5-HT transporter availability predicts amygdala reactivity in vivo. *Journal of Neuroscience, 27*, 9233–9237.

Sergerie, K., Chochol, C., & Armony, J. L. (2008). The role of the amygdala in emotional processing: a quantitative meta-analysis of functional neuroimaging studies. *Neuroscience and Biobehavioral Reviews, 32*, 811–830.

Simpson, J. R., Ongur, D., Akbudak, E., Conturo, T. E., Ollinger, J. M., Snyder, A. Z., et al. (2000). The emotional modulation of cognitive processing: an fMRI study. *Journal of Cognitive Neuroscience, 12* (Suppl 2), 157–170.

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J., Johansen-Berg, H., et al. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage, 23*(Suppl 1), S208–S219.

Stapley, B. J., & Benoit, G. (2000). Biobibliometrics: information retrieval and visualization from co-occurrences of gene names in Medline abstracts. Proceedings of the Pacific Symposium on Bio-computing, 529–540.

Talairach, J., & Tournoux, P. (1988). *Co-planar stereotaxic atlas of the human brain*. New York: Thieme Medical.

Van Horn, J. D., Grethe, J. S., Kostelec, P., Woodward, J. B., Aslam, J. A., Rus, D., et al. (2001). The Functional Magnetic Resonance Imaging Data Center (fMRIDC): the challenges and rewards of large-scale databasing of neuroimaging studies. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 356*, 1323–1339.

Whalen, P. J., Rauch, S. L., Etcoff, N. L., McInerney, S. C., Lee, M. B., & Jenike, M. A. (1998). Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *Journal of Neuroscience, 18*, 411–418.

Wilkowski, B., Szewczyk, M., Rasmussen, P. M., Hansen, L. K., & Nielsen, F. A. (2009a). Coordinate-based meta-analytic search for the SPM neuroimaging pipeline. Paper presented at the International Conference on Health Informatics, Portugal, 2009.

Wilkowski, B., Szewczyk, M., & Hansen, L. (2009b). Bridging the gap between coordinate-and keyword-based search of neuroscientific databases by UMLS-assisted semantic keyword extraction. Neuroimage 47, S165, Presented at the 15th Annual Meeting of the Organization for Human Brain Mapping, June 18–23, 2009, San Francisco.

Williams, L. M., Das, P., Liddell, B. J., Olivieri, G., Peduto, A. S., David, A. S., et al. (2007). Fronto-limbic and autonomic disjunctions to negative emotion distinguish schizophrenia subtypes. *Psychiatry Research, 155*, 29–44.

Wright, C. I., Martis, B., Shin, L. M., Fischer, H., & Rauch, S. L. (2002). Enhanced amygdala responses to emotional versus neutral schematic facial expressions. *Neuroreport, 13*, 785–790.

Yue, P., Melamud, E., & Moult, J. (2006). SNPs3D: candidate gene and SNP selection for association studies. *BMC Bioinformatics, 7*, 166.

Zhu, S., Okuno, Y., Tsujimoto, G., & Mamitsuka, H. (2007). Application of a new probabilistic model for mining implicit associated cancer genes from OMIM and medline. *Cancer Informations, 2*, 361–371.