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## **Systematic Literature Search: Functional Neuroimaging of Geriatric Schizophrenia**

### *ABSTRACT*

*Background:* Previous investigators have used functional Magnetic Resonance Imaging (fMRI) to study the pathophysiology of schizophrenia. To date, no one has exclusively focused on fMRI with geriatric schizophrenia. *Method:* We described three systematic PubMed search strategies on the following topics: (1) geriatric schizophrenia, cognition and dementia; (2) an imaging paradigm designed to elicit an orienting response (i.e., the “oddball” paradigm), schizophrenia, dementia, and (3) fMRI studies using independent components analysis. *Results (Critical Appraisal):* The first search strategy resulted in a large number of sources. We described the rationale for further reduction of this list to find the most relevant 106 sources. The second and third search strategies resulted in 149 and 15 sources, respectively. *Conclusion:* We developed systematic and reusable PubMed search strategies to yield articles relevant to the imaging literature in geriatric schizophrenia.

### *BACKGROUND*

The CTSC’s MSCR program encourages students to conduct systematic literature searches for their thesis projects. We also plan to use this literature search for scientific proposal for an NIH K-23 grant. The focus of the proposed project is an fMRI study on geriatric schizophrenia and cognitive impairment. These searches must locate literature that addresses the following areas:

1. Geriatric schizophrenia, cognition, and dementia
2. Schizophrenia, dementia, and an imaging paradigm designed to elicit an orienting response (i.e., the “oddball” paradigm)
3. Schizophrenia, dementia, and fMRI studies using independent components analysis

The “oddball” paradigm is an imaging paradigm that elicits the “orienting” response and positive amplitude at 300 milliseconds in the event-related potential literature. In the auditory oddball task, the subject hears a “standard” tone 80% of the time. The subject responds to a higher pitched “target” while ignoring “novel” tones such as bells and whirring noises. Both novel and target tones occur with a frequency of 10% during the experimental run.

Independent component analysis is a novel data analysis method used for fMRI, genetic studies, and other large data sets. Independent component analysis is a method of blind source separation that differentiates signal mixtures into independent components or source signals. Independent component analysis is related to but distinctly different from principal component analysis and factor analysis.

### *METHODS: SEARCH STRATEGIES*

We performed a systematic PubMed search strategy to three different searches. These searches represented different levels of difficulty. If the search was simple, we applied only the initial part of this strategy. If the search was complex, we applied the entire search strategy.

We collected several key papers in each domain as recommended by established investigators in this field [1-6]. For a quality control measure, the final search strategy of each domain had to include these selected sources. We used PubMed’s MeSH database to identify the Medical Subject Headings (MeSH) terms and qualifiers most appropriate for the topic of interest. We started with a broad search using these MeSH terms. If articles were missing, we used PubMed’s Single Citation Matcher to identify the sources recommended by expert investigators. We changed the display to citation mode to find all of the MeSH terms associated with these sources. We then incorporated these MeSH terms into another search. If the results of the second search included too many irrelevant sources, we changed the results of this PubMed search to citation mode, allowing us to see the MeSH terms associated with each article. We identified MeSH terms associated with irrelevant articles. We used these MeSH terms to exclude irrelevant articles in the final search. We used the Boolean operators “AND” and “OR” to include MeSH terms taken from the relevant articles followed by the Boolean operator “NOT” to exclude MeSH terms taken from the irrelevant articles from our second search results. We described the results of the final search strategy in a separate heading for each of our three research questions.

### 1. Geriatric Schizophrenia, Cognition, and dementia

On August 10, 2008, we searched PubMed with the following search strategy: "Schizophrenia"[Mesh] AND "Cognition"[Mesh]. This search resulted in 1678 sources. We further narrowed this search by using the following limits: humans, English language, and age > 65 years. This reduced the number of sources to 127. A quick scan of these sources did not reveal a relevant source [1] acquired from a previous, less-systematic PubMed search.

Using PubMed’s Single Citation Matcher, we located one of the key articles [1]. To determine what MeSH terms were assigned to this article, we changed the PubMed display to citation mode. Using a similar process, we determined what MeSH terms were associated with a second [2] and a third source [3]. Ignoring the considerable overlap, the relevant MeSH terms associated with these sources [1-3] are summarized in Table 1.

Table 1, Summary of MeSH terms associated with relevant sources [1-3]

Harvey, 99 [1]	Friedman, 99 [2]	Harvey, 2003 [3]
Age Factors, Aged,	Activities of Daily	Cognition Disorders/etiology*
Aging/psychology*	Living/psychology*	Neuropsychological Tests
Alzheimer Disease/diagnosis*	Alzheimer Disease/pathology	Schizophrenia/complications*
Alzheimer Disease/psychology*	Brain/pathology	
Cognition Disorders/diagnosis*	Cognition Disorders/pathology	
Cognition Disorders/epidemiology	Disease Progression	
Cognition disorders/psychology		
Geriatric Assessment		
Schizophrenia/diagnosis*		
Schizophrenia/psychology		

Next, we explored the MeSH terms “Alzheimer Disease” and “Cognition Disorder” in the MeSH Database. These terms were subsumed in the MeSH tree under the broad MeSH term “Delirium, Dementia, Amnestic, Cognitive Disorders”. To be more inclusive, we decided to use the broader MeSH term. We also explored the MeSH term “Schizophrenia”. This term was included under “Schizophrenia and disorders with psychotic features”. This search was focused on schizophrenia as opposed to the wide range of psychotic disorders. Therefore, we decided to use the more narrow MeSH term “schizophrenia”. The MeSH term “Disease progression” was defined as “the worsening of a disease over time... this concept is most often used for chronic and incurable diseases where the stage of the disease is an important determinant of therapy and prognosis”. This term was particularly relevant to our research question, but this term was only included with one of the relevant sources [2]. Including this term with the Boolean operator

“AND” excluded relevant sources [1, 3]. The MeSH term “aged” was defined as “a person 65 through 79 years of age”. Although this term was included with the three above sources, this age range was too restrictive for a study of late-life schizophrenia. We chose to restrict this age range with the PubMed limits function.

We reviewed the relevant MeSH terms associated with these articles and noted that they both contained the MeSH term “Schizophrenic Psychology”. This term was included under the “Behavioral Conditions and Disciplines”. This MeSH tree did not include “Schizophrenia”. On September 5, 2008, we conducted another PubMed search as follows: (“Schizophrenic Psychology”[Mesh] OR “Schizophrenia”[Majr] AND “Delirium, Dementia, Amnestic, Cognitive Disorder”[Majr] NOT “Adolescent”[Mesh]). We restricted this search to the following limits: Humans, English and Aged + 65 years. We found 382 sources. After changing the display to citation mode, we noted several irrelevant sources with other psychiatric diseases. We added these psychiatric diseases to the final PubMed search with the Boolean operator “NOT”.

#### *Final Search*

On September 7, 2008, we conducted the final PubMed search as follows:

**((((“Schizophrenic Psychology”[Mesh] OR “Schizophrenia”[Majr]) AND “Delirium, Dementia, Amnestic, Cognitive Disorders”[Majr]) NOT “Adolescent”[Mesh]) NOT “Bipolar Disorder”[Mesh]) NOT “Personality Disorders”[Mesh]) NOT “Stress Disorders, Traumatic”[Mesh]) NOT “Substance-Related Disorders”[Mesh].** Using the aforementioned limits, we found 337 sources from 1965 to present with this search. This search included the three aforementioned sources [1-3]. We changed the display to citation mode and did not observe any frequently occurring MeSH terms that could have further reduced the number of sources without excluding relevant sources.

## **2. Schizophrenia, dementia, and the “oddball paradigm”**

Using the MeSH Database, we searched “evoked potentials”. Under “evoked potentials”, the MeSH Database included the term “event-related potentials, P300”. This term was more relevant and specific to the proposed research question. On August 24, 2008, we conducted a search as follows: “Event-Related Potentials, P300”[Mesh] AND “Dementia”[Mesh]. We found 80 references with this search. Applying the limits “Humans” and “English”, we further reduced the results to 62 references. We determined that the vast majority of these sources were relevant to the proposed research question.

We applied the same search strategy to schizophrenia. On August 24, 2008, we conducted the following search: “Event-Related Potentials, P300”[Mesh] AND “Schizophrenia”[Majr]. This search resulted in 166 sources. We applied the limits “Humans” and “English” to further reduce the search to 147 sources. The limit “Middle Aged + Aged: 45+ years” further reduced the number of sources to 59. We determined that the vast majority of these sources were relevant to the proposed research questions. This search also contained several meta-analyses for a synthesis of the research in this area [4, 6].

#### *Final Search*

To keep the methods parallel with the subsequent search, we combined the two searches into a single search. On September 7, 2008, we completed the following search:

**“Schizophrenia”[Majr] OR “Dementia”[Majr] AND “Event-Related Potentials, P300”[Majr].** After applying the limits “Humans” and “English”, we found 149 highly relevant sources from 1993 to present. We changed the display to citation mode. We did not find any MeSH terms that could be excluded to further narrow this search without eliminating the highly relevant sources.

### 3. Schizophrenia, dementia, and fMRI studies using independent components analysis

We did not find any MeSH terms that would describe independent component analysis, so we did not perform the initial controlled vocabulary (MeSH) search described previously in this methods section. We used Single Citation Matcher to retrieve a previously identified source [5] and changed the display to citation mode. This article was associated with the following relevant MeSH terms summarized in table 2.

Table 2, Summary of MeSH terms associated with relevant source [5]

Garrity, 2007 [5]
Image Processing, Computer-Assisted;
Magnetic Resonance Imaging/statistics & numerical data
Models, Neurological; Neural Pathways/physiopathology*
Principal Component Analysis
Schizophrenia/diagnosis
Schizophrenia/physiopathology*
Schizophrenia Psychology*

The list of MeSH terms listed with this reference included “principal component analysis”. We described in the background section that principal component analysis was defined differently as a different method of blind source separation than independent component analysis. We decided to use the text words “independent components analysis”. On September 5, 2008, we conducted the following PubMed search: “Schizophrenia”[Majr] OR “Delirium, Dementia, Amnesic, Cognitive Disorders”[Majr] and “independent component analysis”[tw]. We found 85 sources with this search including a large number of genetics studies not relevant to this proposed research question.

#### *Final Search*

On September 5, 2008, we conducted a final PubMed search: (**"Schizophrenia"[Majr] OR "Dementia"[Majr] NOT "Genotype"[Mesh] AND "independent component analysis"[tw]**). We found 15 sources from 2004 to the present date. This list included the previously identified source [5]. We changed the display to citation mode. We did not identify any irrelevant MeSH terms in citation mode to reduce this list any further.

#### *METHODS: CRITICAL APPRAISAL*

The first search was relatively complex and required us to utilize our entire search strategy as described in the methods section. Our final search result was relatively large with 337 sources from 1965 to the present. We reviewed all of these sources and sent the most relevant sources to the PubMed clipboard. The inclusion criteria for this search consisted of the words “old”, “older”, “late-life”, and “geriatric” in the title of the article. We expanded the criteria to include studies assessing the differences of schizophrenia and a neurodegenerative disease such as Alzheimer’s disease. We sent a total of 106 sources to clipboard for further review. These sources included the initial sources [1-3]. The remaining 103 sources were relevant to the proposed research question.

The second search was relatively simple. This search focused on schizophrenia, dementia, and event related potentials. Our initial search with PubMed’s MeSH Database included our recommended source. This research modality has a 30-year history in dementia and schizophrenia research. The large number (149) of sources in the final search reflected this long history and included sources from 1993 to the present. We reviewed these sources. The vast majority of these sources were relevant to the research question. We did not need to refine this search any further with additional MeSH terms.

The third search focused on a novel fMRI data-analysis technique called independent components analysis. The newness of this technique was reflected by the omission of independent components analysis from the MeSH Database. After electing to use the text word “independent component analysis” and excluding genetic studies, we found a very small list of references (15 sources from 2004 to the present). To our knowledge, this list includes all of the sources using independent component analysis with schizophrenia and dementia.

### *CONCLUSION*

This paper detailed the evolution of three search strategies for our research interests. We ensured that each search included relevant sources as recommended by experts in the field of schizophrenia and fMRI utilizing the PubMed MeSH Database as a topical guide. The net result is a reusable set of PubMed queries. We plan to use the final queries to quickly and easily execute systematic PubMed queries on these topics for the thesis project and for the scientific proposal for a K23 career-training grant. Other investigators are encouraged to use and refine these queries for similar research interests.

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