

# Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring

## Convergent regional brain abnormalities in behavioral variant frontotemporal dementia: a neuroimaging meta-analysis of 73 studies

--Manuscript Draft--

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<b>Abstract:</b>	<p><b>INTRODUCTION:</b> Numerous studies have reported brain alterations in behavioral variant frontotemporal dementia (bvFTD). However, they pointed to inconsistent findings.</p> <p><b>METHODS:</b> We used a meta-analytic approach to identify the convergent structural and functional brain abnormalities in bvFTD. Following current best-practice neuroimaging meta-analysis guidelines, we searched PubMed and Embase databases and performed reference tracking. Then, the coordinates of group comparisons between bvFTD and controls from 73 studies were extracted and tested for convergence using activation likelihood estimation.</p> <p><b>RESULTS:</b> We identified convergent abnormalities in the anterior cingulate cortices, anterior insula, amygdala, paracingulate, striatum, and hippocampus. Task-based and resting-state functional connectivity pointed to the networks that are connected to the obtained consistent regions. Functional decoding analyses suggested associated dysfunction of emotional processing, interoception, reward processing, higher-order cognitive functions, olfactory and gustatory perceptions in bvFTD.</p> <p><b>DISCUSSION:</b> Our findings highlighted a key role of the salience network and subcortical regions in the pathophysiology of bvFTD.</p>

22.11.2021

Dear Prof. Liana G. Apostolova

Editor-in-Chief,

*Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*

We would like to submit our manuscript entitled "**Convergent regional brain abnormalities in behavioral variant frontotemporal dementia: a neuroimaging meta-analysis**" to be considered for publication in *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*.

During the last decades, numerous neuroimaging studies identified brain alterations in patients with behavioral-variant frontotemporal dementia (bvFTD) in order to unravel its neurobiological mechanisms. However, the available studies point to diverse and often conflicting findings. The current quantitative meta-analysis aims to elucidate converging structural and functional patterns of abnormality in bvFTD across previous studies. In this meta-analysis, we identified convergent regional abnormalities in the anterior cingulate cortices, anterior insula, amygdala, paracingulate, striatum, and hippocampus. Task-based co-activation patterns and resting-state functional connectivity pointed to the joint networks that are connected to the obtained regions. Hierarchical clustering analysis demonstrated two sub-networks of the identified consistent regions, namely the insula-amamygdala network and the cingulo-striatal network. Functional characterization of the convergent regions suggested associated dysfunction of emotional processing, interoception, reward processing, higher-order cognitive functions, olfactory and gustatory perceptions in bvFTD.

We believe that this revisited meta-analysis in bvFTD will be of special interest to the readers of *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring* due to the following reasons: i) we followed the best-practice guideline to conduct a standard neuroimaging meta-analysis in terms of search strategy, selection criteria, and statistical analysis; ii) this is a large-scale meta-analysis including 73 individual studies; iii) we included both structural and functional neuroimaging experiments; iv) we performed different sets of complementary analyses such as task-based and resting-state functional connectivity, functional decoding, and hierarchical analysis to provide overarching perspectives on pathophysiology of bvFTD.

All authors have contributed to the manuscript and have approved its final version. Authors have no conflicts of interest to disclose. This manuscript is not under simultaneous consideration by another publisher, and has not been published previously in whole or substantial part. We are grateful in advance for your consideration.

Sincerely yours,

Masoud Tahmasian & Simon B. Eickhoff, on behalf of all authors

05.03.2022

Dear Prof. Liana G. Apostolova

Editor-in-Chief,

Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring

Re: manuscript "Convergent regional brain abnormalities in behavioral variant frontotemporal dementia: a neuroimaging meta-analysis", DADM-D-21-00251R1

We would like to thank you and the reviewers for the careful assessment of our manuscript. We found the comments very insightful and constructive, and have attempted to address them to the best of our ability. Please see below for a point-by-point response to each comment, along with the changes made in the manuscript. The manuscript file is also revised accordingly, and the changes are highlighted. We hope that we have properly responded to the reviewers' comments and concerns, and we are looking forward to hearing their assessment on the revised manuscript.

Once again, thank you very much for your consideration.

Sincerely yours,

Masoud Tahmasian & Simon B. Eickhoff, on behalf of all authors

**Reviewer #1:**

I had the opportunity to revise the manuscript by Kamalian A et al that used a meta-analytic approach to study bvFTD considering both structural and functional brain studies on bvFTD. The paper is well-written and the results section is clear and straightforward. The Discussion section is really detailed providing a very systematic description of clinical-neuroanatomical correlation of the present findings in related to bvFTD disease. Overall, the manuscript is really interesting in the field of neurodegenerative dementias, adding significant knowledge and providing a robust example of the application of this meta-analytic approach also to a non-Alzheimer's dementia.

R: We would like to thank the reviewer for the useful recommendations, which we were happy to incorporate in the revised version.

I only have a couple of minor comments:

1. As stated in the first sentence of the Discussion, a decade has passed since the revision of the diagnostic criteria for bvFTD. In your sample, a subgroup of studies that used Neary and/or McKhann diagnostic criteria has been considered. Although the overall number of patients is small, I wonder if a subgroup analysis can be considered: it might be interesting to see the "neuroanatomical effect" of the evolution of diagnostic criteria for bvFTD.

R: Performing sub-analysis on various diagnostic criteria makes a lot of sense, but unfortunately in this study, 22 experiments used the Raskovsky criteria and only 12 experiments used Neary criteria. Thus, the comparison between these two conditions is statistically not meaningful, as the minimum required number of experiments in each ALE analysis for obtaining 80% statistical power should be more than 17 experiments (Eickhoff, Nichols et al. 2016).

2. This study supports the feasibility of meta-analytic analysis also in FTD and (bvFTD in particular): by applying specific inclusion/exclusion criteria, 73 studies with 1672 bvFTD patients and 3884 healthy participants have been identified and used. On the other hand, as is known 40% of FTD patients have a family history of dementia, and

about 20% have a clear autosomal dominant inheritance. From this point of view, the presymptomatic phase of FTD (considering mutation carriers of the main causative genes: C9ORF72, GRN, MAPT) has been explored in different studies worldwide. Even if the number of subjects included does not yet allow a meta-analytic approach, it might be interesting to have an account of the "state of the art" (number of studies, number of subjects included for the different mutations ...) also for presymptomatic FTD.

R: Many thanks for suggesting this issue. In the revised version, we have added a column in Table S1, which reports the genetic and histopathologic status of patients, if they are reported in the original publications. Of note and as it is evident from the table, only a few studies reported such data. However, the numbers are not enough to run separate ALE and our meta-analysis was mainly focused on clinically diagnosed bvFTD patients, and focusing on the presymptomatic bvFTD is out of the scope of this manuscript. Regarding your suggestion to work on presymptomatic bvFTD (genetically susceptible individuals), we mentioned this suggestion in the future direction section (Section 4.4, page 17), as follows:

*"Looking further into the neurological and neuroimaging markers of genetically susceptible individuals (e.g. C9ORF72 expansion carriers) might give us invaluable insight into onset and pathophysiology of bvFTD."*

## **Reviewer #2:**

This neuroimaging meta-analysis by Kamalian and colleagues compiles relevant data about structural and functional brain abnormalities in behavioral variant frontotemporal dementia patients. The procedures for the selection of papers are adequately accomplished. However, some important information should still be included:

R: We are very grateful for all constructive and useful suggestions to our reviewer.

1. Methods: the authors said that "patients with no other major comorbidities" were included in the study. Please specify, either in the manuscript or in the supplemental material what was considered major comorbidities.

R: Thank you for pointing out this issue. Patients with no comorbid psychiatric diagnosis (e.g. major depressive disorder and bipolar mood disorder), other forms of dementia or

neurological symptoms, and no history of alcohol and substance abuse were included in this study. We clarified the exclusion criteria as requested (Section 2.1, page 4), as follows:

*"Studies were included if they (1) included clinically diagnosed bvFTD patients with no concurrent psychiatric diagnosis (e.g. major depressive disorder and bipolar mood disorder), other forms of dementia or neurological symptoms, and no history of alcohol and substance abuse."*

2. In the protocol registered at PROSPERO the author mentioned that quality assessment (risk of bias) analysis would be performed using the Effective Health Practice Project (EPHPP) tool. Please, add to the questions applied and the score of each included study. It is important for the reader to understand the quality of the evidence.

R: The process of quality assessment in neuroimaging field is still controversial. The Newcastle-Ottawa Scale (NOS) and Effective Health Practice Project (EPHPP) are two of the most commonly used criteria to assess the quality of studies in clinical and public health studies. However, after our careful assessment, we found that these criteria are not suitable to assess quality of neuroimaging studies and their analyses effectively. A few neuroimaging meta-analyses, however, have modified these criteria in order to tailor them to neuroimaging studies (Strakowski, DelBello et al. 2000, Gentili, Messerotti Benvenuti et al. 2019, McLachlan, Rai et al. 2020, Su, Gong et al. 2021). Thus, we chose a 10-point checklist, developed by Strakowski and collages (Strakowski, DelBello et al. 2000) and has been adopted afterwards in recent neuroimaging meta-analyses (Strakowski, DelBello et al. 2000, Su, Gong et al. 2021). We added the quality appraisal section to Section 2.1 (page 5) as follows:

*"We used a 10-point checklist developed by Strakowski et al. [17] and employed by previous meta-analyses to assess individual study quality based on imaging methodology and clinical and demographic properties of the study [18-20]. The quality assessment score of included studies are reported in Table s1."*

We also added the scores of each included study to Table S1.

3. I recommend reporting either in figure 1 or the results section the number of papers separated retrieved in PubMed and Embase. Also, double-check the number of records after removing duplicates as there are divergent numbers reported in the text and the figure.

4. Figure 1 mentions the additional inclusion through other sources. Please, specify it.

R 3-4: According to this comment, we provided the number of entries from PubMed and EMBASE in Figure 1 separately and also corrected the record number after duplicate removal. The additional inclusion is also now specified in the Figure 1.

5. The authors should include a statistical measure of heterogeneity among the included studies.

R: Regarding the statistical measure of heterogeneity, there is no established approach for this akin to behavioral effect-size meta-analyses. The way this is usually handled in CBMA is diagnostics (the contribution analysis) and target sub-analyses with more homogeneous sets of studies. This issue has been added to the limitation part in page 16, as follows:

*"Finally, two methodological limitation of our meta-analysis, which are common to all CBMA methods, were that 1) pooling of findings was based on the peak coordinates of significant regions, which essentially ignores the volume and extent of clusters; 2) conventional ALE analysis could miss out biological heterogeneity."*

6. As the authors mentioned, there are samples from genetic and histopathological subtypes of bvFTD among the studies included. Although it is not enough to perform subgroup analysis, the authors could include in the demographics table (Table S1) this information (when available).

R: We have included a new column in Table S1, which reports the genetic and histopathologic status of patients, if they have been reported in the original publications.

**Reviewer #3:**

In this paper Kamalian and colleagues perform a voxel-wise multimodal neuroimaging analysis from studies focusing on differences between behavioral variant forms of frontotemporal dementia (bv-FTD) and age-matched healthy controls. They performed a review of literature and from the relevant studies (31 after merging 73 publications where overlapping data was used), extracted relevant MNI/Talairach coordinates from each study to determine if there were convergent changes in terms of grey matter volume from structural MRI, in/decreases in metabolism from FDG PET or changes in connectivity based on either task-based or task-free functional MRI. Their analysis revealed 5 regions that survived corrections for multiple comparisons using cluster-based Family Wise Error rate. These regions covered amygdala/hippocampus, caudate/striatum, paracingulate gyrus and medial frontal regions, and the anterior insular cortex. Next they inserted these seed regions into healthy task-free and task-based databases to determine what other brain regions that had connectivity with these seed regions, as well as what functions these regions and networks were known to be involved in. The resulting maps led to a significant involvement of the salience network, a brain network for the interpreting, processing, and handling emotion In addition, there were implications of executive dysfunction and amnestic presentations with regards to changes in the hippocampus and medial temporal lobe structures.

R: We would like to thank the reviewer for her/his benevolent assessment and the suggestions.

**COMMENTS:**

1. Table S1 - the first entry indicates that it included individuals with an autosomal dominant form of FTD caused by a mutation in C9ORF72. The authors have made a note about familial forms of bv-FTD having a role in the findings as part of the discussion, but it would be helpful, if the data is available, to clarify if studies included familial cases or not within their bv-FTD group.

R: As mentioned in response to the comments of R1 and R2, we have included a new column in Table S1, which reports the genetic and histopathologic status of patients, if they have been reported in the original publications.

2. Table S1 - The authors state in the main text that there was one t-fMRI study, but I could not find it listed in the table. Please could the authors state which one it was?

R: Many thanks for noticing the lapsus calami. Now, we revised the table as Augustus 2015 is actually the mentioned task-based fMRI study.

3. Section 2.1 - Check numbering of inclusion criteria

R: We corrected the numbering, as suggested.

4. Section 2.1 - How many studies were excluded for seed-based FC, DTI, and cortical thickness? I know this is covered by Table S2, but a summary of these exclusions as part of the methods or results section in the main manuscript would be helpful to the reader.

R: We added a summary of exclusion reasons in the manuscript (Section 3.1, page 6) and also added the detailed number of excluded studies and the reasons in Figure 1.

*"Of the 495 studies excluded by full-text screening from both electronic databases and reference checking, 124 were excluded because the subjects were not bvFTD patients, 97 were excluded because they did not report coordinates significantly different between two groups, and 78 were excluded due to using regions of interest (detailed reasons for exclusion are reported in Figure 1)."*

5. I'm interested in finding out a bit more in terms of how MNI and Talairach space was handled. Presumably many of these studies would each generate their own study specific templates. While these templates may be globally oriented to one of these stereotactic frames, it is much less likely to be well-aligned at the cortical level due to the atrophy present in the bvFTD group. How is this handled, is it just part of the uncertainty that is implied by using the Gaussian kernel with varying degree FWHM in the ALE?

*R: The conversion between MNI and Talairach is handled by the well-established and validated tal2icbm tools. However, we agree that this is an important general limitation on geriatric brain disorders. The optimal registration to a standard space is more challenging in these populations, and may lead to errors in some cortical regions. While we acknowledge this, this problem already exists at the level of the original studies. We are not able to rectify the issue at the meta-analytic level, and there exists no established method of incorporating the uncertainty imposed by sub-optimal registration in the ALE meta-analysis, including adjustment of the Gaussian kernel. However, an important goal of ALE meta-analysis is to consolidate over multiple experiments and identify convergent effects that are robust to random (but not systematic) errors, such as those that may have been caused by mis-registration. For any comparison between patients and controls in ALE meta-analysis, all images need to be in the same reference space (i.e., MNI). Meta-analyses are then just examining whether the current literature, i.e., the coordinates in standard space converge.*

6. Results - The paracingulate cortex is abbreviated as PrCC in the Figures, but this is not mentioned in the text as well, and it might be useful to have it there as well when talking about the main five seeds from the ALE.

*R: The abbreviation is now added in the Discussion section (page 10), where this region is first discussed:*

**"We performed a large-scale CBMA on both structural and functional brain studies on bvFTD, nearly a decade after the revision of its diagnostic criteria and found consistent abnormalities in the five clusters including the AIC, ACC, paracingulate cortex (PrCC), subcallosal cortex, striatum, amygdala, and anterior hippocampus in patients with bvFTD compared to healthy subjects."**

7. Figure 4 - I'm a bit confused as to how the two PrCC seed regions could be so highly correlated with each other, yet they are correlated in opposite directions with the Anterior Insular Cortex (from color bars looks to be +/-0.5)?

*R: Neurobiologically, the pattern of connectivity across the anterior cingulate and paracingulate cortices is heterogeneous, and this also involves different patterns of*

*connectivity to insula across these regions (Margulies, Kelly et al. 2007, Stevens, Hurley et al. 2011, Zhou, Shi et al. 2016) . Theoretically, it is possible for two correlated variables (X and Y) to show diverging correlations to a third variable (Z) if for example X is dependent on Y and Z, but Y and Z are independent. In other words, the three regions are each a different entity with their own unique connections to various brain regions and although the two PrCC seed regions are highly correlated with one another, one of them seems to be connected to the anterior insula cortex and the other is not.*

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## **Convergent regional brain abnormalities in behavioral variant frontotemporal dementia: a neuroimaging meta-analysis of 73 studies**

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**Running title:** Neuroimaging Meta-analysis in bvFTD

**Keywords:** Behavioral Variant Frontotemporal Dementia; Activation Likelihood Estimation; Meta-Analytic Connectivity Modeling; Resting State Functional Connectivity; Hierarchical Clustering; Functional Decoding

## **Abstract**

**INTRODUCTION:** Numerous studies have reported brain alterations in behavioral variant frontotemporal dementia (bvFTD). However, they pointed to inconsistent findings.

**METHODS:** We used a meta-analytic approach to identify the convergent structural and functional brain abnormalities in bvFTD. Following current best-practice neuroimaging meta-analysis guidelines, we searched PubMed and Embase databases and performed reference tracking. Then, the coordinates of group comparisons between bvFTD and controls from 73 studies were extracted and tested for convergence using activation likelihood estimation.

**RESULTS:** We identified convergent abnormalities in the anterior cingulate cortices, anterior insula, amygdala, paracingulate, striatum, and hippocampus. Task-based and resting-state functional connectivity pointed to the networks that are connected to the obtained consistent regions. Functional decoding analyses suggested associated dysfunction of emotional processing, interoception, reward processing, higher-order cognitive functions, olfactory and gustatory perceptions in bvFTD.

**DISCUSSION:** Our findings highlighted a key role of the salience network and subcortical regions in the pathophysiology of bvFTD.

**Keywords:** Behavioral Variant Frontotemporal Dementia; Activation Likelihood Estimation; Meta-Analytic Connectivity Modeling; Resting State Functional Connectivity; Hierarchical Clustering; Functional Decoding.

## **1. INTRODUCTION**

Behavioral-variant frontotemporal dementia (bvFTD) is a neurodegenerative syndrome characterized by neurodegeneration in the frontal and anterior temporal lobes leading to insidious and progressive changes in behavior, personality, and social functions [1]. BvFTD is the most common frontotemporal dementia (FTD) syndrome and the second major cause of early-onset dementia after Alzheimer's disease (AD) [1]. Given the heterogeneous symptomology and gradual course of the disease, early detection of bvFTD is often abstruse and causes frustrating experiences for patients and relatives [2]. Accordingly, the current bvFTD diagnostic criteria has incorporated neuroimaging findings to improve the accuracy of clinical evaluation particularly in early stages [3].

The most identified structural and functional brain changes in early stages of bvFTD target a group of interconnected brain regions, so-called "salience network" (SN), which is associated with social-emotional processing [1]. However, individual neuroimaging studies in bvFTD point to divergent findings due to heterogeneous clinical samples, diversity of imaging modalities, flexible analyses, and statistical methods. Thus, quantitative assessment of neural abnormalities using neuroimaging meta-analysis is needed to overcome such divergence in the bvFTD literature [4, 5]. There are few prior bvFTD neuroimaging meta-analyses that indicated atrophy, hypoconnectivity, and hypometabolism in a wide number of brain regions covering the frontomedial cortex, basal ganglia, anterior insula, and the temporal cortex [6-8]. However, these previous meta-analyses were mostly unimodal (i.e., including only VBM experiments, FDG-PET, or resting-state fMRI (rs-fMRI)) [6-8], included a low number of patients, various selection criteria, and often used liberal statistical methods (e.g., FDR), which increases the opportunity for false positive results [9]. Moreover, previous meta-analyses have pooled only structural studies, highlighting the role of SN in bvFTD. Thus, a multimodal meta-analysis, including functional imaging results, might provide more information in pathophysiology of bvFTD.

In order to elucidate consensus structural and functional regional aberrations in bvFTD, we applied activation likelihood estimation (ALE), the most commonly applied algorithm among the coordinate-based meta-analysis (CBMA) methods, which assesses regional convergence between foci obtained from group comparison experiments [10]. Next, we located brain co-activation patterns using meta-analytic connectivity modeling (MACM) [11] and resting-state functional connectivity (RSFC) [12] to reveal networks connected to the meta-analytically obtained regions in task-based and resting-state experiments, respectively. Finally, we performed hierarchical clustering analysis based on the pairwise RSFC profile and functional decoding of the convergent clusters to reveal sub-networks between convergent regions and assess the mental functions associated with these regions, respectively. We assessed functional characteristics of the identified regions using the BrainMap dataset [13].

## 2. METHODS AND MATERIALS

The present large-scale CBMA was performed following the recently-developed, best-practice guidelines for neuroimaging meta-analyses [4, 5] and adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [14, 15]. The protocol for this study was pre-registered based on the International Prospective Register of Systematic Reviews (PROSPERO, code: CRD42020127902).

### 2.1. Search strategy, selection criteria, and quality appraisal

We performed a systematic literature search (up to May 2020) to identify structural and functional neuroimaging studies that compared bvFTD patients with their matched healthy controls (details are reported in the supplement). Studies were included if they (1) included clinically diagnosed bvFTD patients with no concurrent psychiatric diagnosis (e.g. major depressive disorder and bipolar mood disorder), other forms of dementia or neurological

symptoms, and no history of alcohol and substance abuse [3, 16]; (2) included at least six participants in either patient or healthy group; (3) used VBM, fMRI (resting-state or task based), and FDG-PET as the imaging modality; (4) reported the coordinates of between-group contrasts in a defined stochastic space (i.e., Montreal Neurological Institute [MNI] or Talairach); and (5) performed a whole-brain analysis. Thus, studies using seed-based FC, DTI, and cortical thickness methods were all excluded, as suggested previously [4, 5].

We used a 10-point checklist developed by Strakowski et al. [17] and employed by previous meta-analyses to assess individual study quality based on imaging methodology and clinical and demographic properties of the study [18-20]. The quality assessment score of included studies are reported in Table S1.

## 2.2. Activation likelihood estimation analysis

The revised ALE algorithm was used to identify convergent patterns of brain alterations by showing a convergence of reported coordinates across experiments, which is higher than expected under a random spatial association [10]. The experiments were categorized by their effect direction (in-/decreases) and imaging modalities (see the supplement for details). Separate ALE meta-analyses were performed on four subsets of the experiments: (i) pooling all experiments together, (ii) experiments reporting decreases in activity/connectivity, metabolism or grey matter volume (Control > bvFTD), (iii) VBM experiments, and (iv) combination of functional imaging (FDG-PET, rs-fMRI, t-fMRI) experiments. The other sets of experiments, including experiments categorized based on diagnostic criteria, did not reach the minimum required number of experiments for sufficient power ( $\geq 17$ ) [9].

## 2.3. Meta-analytic connectivity modeling (MACM) and resting-state functional connectivity (RSFC)

We investigated the task-based and task-free functional connectivity profiles of the obtained regions using MACM [11] and RSFC [12], respectively. MACM analysis uses task-based functional neuroimaging studies to meta-analytically identify regions that are co-activated across a range of different tasks with the seed regions, whereas RSFC identifies task-free FC patterns of the convergent meta-analytic clusters. A more detailed description of each analysis is available in the Supplement.

#### **2.4. Hierarchical clustering (HC) and functional decoding (FD)**

We performed HC analysis based on the pairwise RSFC profile of the identified regions to reveal the sub-networks associated with the convergent regions. Finally, we assessed the functional characteristics of the identified regions using the BrainMap dataset [13]. Detailed description of each analysis is available in the Supplement.

### **3. RESULTS**

#### **3.1. Experiments included in the meta-analysis**

After removing duplicate records, we screened a total number of 5,045 abstracts and included 73 studies in our meta-analysis (Figure 1, Table S1). The excluded studies and the reasons of exclusion are reported in Table S2. Of the 495 studies excluded by full-text screening from both electronic databases and reference checking, 124 were excluded because the subjects were not bvFTD patients, 97 were excluded because they did not report coordinates significantly different between two groups, and 78 were excluded due to using regions of interest (detailed reasons for exclusion are reported in Figure 1). Among the included papers, 27 studies were performed based on the FRONTIER open dataset and thus, their data were merged to minimize within-group effects [4]. In addition, eight other studies had partially overlapping samples, and they were pooled together as well. Finally, 31 independent experiments (out of 73 studies) comprising 1,672 bvFTD patients and 3,884 healthy participants were used for ALE analysis.

These experiments include VBM ( $N = 20$ ), t-fMRI ( $N = 1$ ), rs-fMRI ( $N = 2$ ) or FDG-PET ( $N = 12$ ). Of note, some experiments used more than one imaging modality; therefore, the collective number of experiments included in each imaging modality exceeds the number of total experiments. Decrease in functional/structural experiments (Controls > bvFTD) was observed more commonly ( $N = 28$ ) and only a few studies ( $N = 3$ ) reported increased functional/structural experiments (bvFTD > Controls).

### **3.2. Convergent regional abnormalities in bvFTD**

First, we assessed consistent structural and functional abnormalities by pooling all experiments ( $N = 31$ ) and identified five convergent clusters in the following regions ( $p < 0.05$ , cFWE): (i) the right amygdala and hippocampus; (ii) the left caudate and subcallosal cortex; (iii) bilateral paracingulate gyrus and anterior cingulate cortex (ACC); (iv) bilateral paracingulate gyrus extending to small portions of the medial orbitofrontal cortex; and (v) the left anterior insular cortex (AIC) extending to frontal orbital cortex (Figure 2A, Table 1a). Most of the included experiments reported "decrease" contrasts (Controls > bvFTD). So, performing ALE analysis on these experiments showed very similar convergent clusters ( $p < 0.05$ , cFWE) (Figure 2B).

Next, we performed separate ALE analyses for the imaging modality by categorizing the experiments to structural ( $N = 21$ ) and functional ( $N = 17$ ). The ALE analysis of structural (i.e., VBM) experiments revealed clusters of convergence in the amygdala and hippocampus, paracingulate gyrus and frontal medial cortex, as well as the AIC and frontal orbital cortex ( $p < 0.05$ , cFWE) (Table 1b, Figure 2C). The location of these clusters corresponded to the first, third, and fifth clusters of the all-experiments analysis respectively, but was smaller in size. Confining the analysis to the functional experiments (i.e., FDG-PET, rs-fMRI, and t-fMRI) demonstrated three significant clusters in the left caudate and accumbens, paracingulate gyrus and ACC and another more rostral region in the ACC ( $p < 0.05$ , cFWE). The last cluster, unlike

the other two, did not correspond to any of the regions identified in the all-experiments analysis (Figure 2C).

### **3.3. Connectivity patterns of the identified convergent regions**

The MACM and RSFC analyses pointed to the joint networks that are connected to the obtained clusters (Figure 3, Figures S1 and S2). The overlap of MACM and RSFC maps revealed significant task-based and task-free co-activation of the amygdala and hippocampus cluster with the striatum, thalamus, fusiform gyrus, inferior frontal gyrus, and midline frontal regions. MACM analysis demonstrated that the amygdala/hippocampus cluster has significant co-activation with the AIC. In addition, RSFC analysis showed additional task-free connectivity of amygdala/hippocampus cluster with the entorhinal cortex, superior and middle temporal gyri, precuneus, posterior cingulate cortex, and cerebellum.

The convergent cluster in the left caudate and subcallosal cortex was associated with the striatum, thalamus, AIC, midline frontal regions, posterior cingulate gyrus, and cerebellum in both MACM and RSFC analyses, but with the superior lateral occipital cortex, and middle temporal gyrus only in task-free analysis, and the left superior parietal lobule and parietal operculum only in task-based analysis.

The rostral paracingulate and frontal medial cortex cluster showed task-based coactivation and RSFC with the medial frontal regions, posterior cingulate cortex, precuneus, hippocampus, amygdala, and superior lateral occipital cortex, but was also functionally connected to the medial thalamus, AIC, Heschl's gyrus, and cerebellum only in RSFC analysis. Most of the significant regions for this cluster in the MACM analysis were also observed in the RSFC analysis.

The more caudal significant cluster in the paracingulate and ACC similarly functionally connected to the medial frontal regions, AIC, striatum, thalamus, middle and inferior frontal gyri, and posterior cingulate cortex in MACM and RSFC analyses, but additionally revealed RSFC

with the cerebellum, and meta-analytic co-activation with the superior parietal lobule and right angular gyrus.

The AIC cluster was functionally connected with the paracingulate gyrus and ACC, striatum, thalamus, middle and inferior frontal gyri, superior parietal lobule, and different regions within the cerebellum during both task and rest. In addition, the AIC showed only task-based functional connectivity with the precentral gyrus, fusiform gyrus, and superior parietal lobule, and RSFC with the temporal pole, Heschl's gyrus, intracalcarine cortex, and lingual gyrus. All these results were corrected for cFWE.

### **3.4. Hierarchical clustering of convergent findings**

To identify functionally coherent sub-networks of the identified consistent regions, we performed hierarchical clustering analysis based on their pairwise RSFC profile. In this analysis, at the first level, we identified two main sub-networks, namely the insula-amygdala network, and the cingulo-striatal network including the ACC, paracingulate cortex, frontal medial cortex, subcallosal cortex, and striatum. The latter was grouped into two additional sub-networks at the second level: one including the two clusters located in the medial frontal lobe, and the other one including the convergent cluster in the striatum and subcallosal cortex (Figure 4).

### **3.5. Functional decoding of convergent clusters**

Our forward-inference functional decoding of the identified regions using the BrainMap database demonstrated their significant involvement in emotional processing, interoception, reward processing, higher-order cognitive functions, as well as olfactory and gustatory perception (Figure 5). More specifically, the amygdala/hippocampus cluster was activated in olfactory perception, processing of negative and positive emotions, and reward processing. The convergent cluster in the left caudate and subcallosal cortex was mostly associated with reward processing, gustatory perception, cognitive reasoning, and sexual interoception. Gustatory

perception and reward processing were also associated with activations in the rostral paracingulate gyrus / frontal medial cortex cluster. The more caudal paracingulate gyrus and the ACC cluster was more likely to be activated in cognitive reasoning and response to rewards. Finally, the AIC was associated with thermal interoception, processing of disgust, and language semantics. All these results were corrected for FDR.

#### 4. DISCUSSION

We performed a large-scale CBMA on both structural and functional brain studies on bvFTD, nearly a decade after the revision of its diagnostic criteria and found consistent abnormalities in the five clusters including the AIC, ACC, paracingulate cortex (PrCC), subcallosal cortex, striatum, amygdala, and anterior hippocampus in patients with bvFTD compared to healthy subjects. These regions predominantly showed decreased gray matter volume, functional hypoactivation, or dysconnectivity, to various degrees in each region. While the abnormalities in the striatum were mainly functional, structural abnormalities were more predominant in the AIC, amygdala, and anterior hippocampus, and midline frontal regions were both functionally and structurally impaired. In addition, we used MACM and RSFC analyses to characterize the connectivity pattern of the convergent regions and observed significant co-activation of them with each other, and with additional brain regions including the thalamus, lateral prefrontal cortex, and association cortices in the parietal lobe. Next, using hierarchical clustering of the convergent regions, we classified them into two main groups: one including the AIC, amygdala, and hippocampus, and the other one including the midline frontal areas and striatum. Moreover, functional decoding analysis showed involvement of the former first set of regions in emotional processing, and of the latter in reward processing and higher-order cognitive functions.

##### 4.1. The key role of the salience network in bvFTD

The cortical layer 5b of AIC and pregenual ACC (pgACC) contains a specialized type of large spindle-shaped projection neurons called von Economo neurons (VEN), which are presumed to be involved in social cognition and self-awareness [21]. The number of these neurons in the AIC and pgACC is significantly depleted in patients with bvFTD [22-24], parallel to clinical severity of bvFTD, and even in the absence of gross atrophy of these regions [21]. Accordingly, histopathological and imaging studies have suggested that the AIC and pgACC are among the earliest atrophied regions in bvFTD [25]. These regions are the key hubs of the SN, which guides behavior in response to the perceived salience of current external/internal events, i.e., their significance for the survival of the individuals [24]. In this network, the AIC and pgACC play distinct, but interdependent roles, acting as afferent (“sensory”) and efferent (“motor”) hubs of the SN, respectively. More specifically, the AIC detects and represents subjective emotional, homeostatic, social, and motivational salience of the immediate environmental or bodily states [26, 27], and the ACC initiates goal-directed behaviors in response to these salient stimuli [28]. Several studies have reported decreased FC within the SN in patients with bvFTD [29]. It is well-documented that the main hubs of the SN can lead to the main characteristic symptoms of bvFTD, including impaired emotional processing and social cognition, disinhibition, executive dysfunction, and apathy.

Impaired emotional recognition is a common symptom in bvFTD and has been reported for different types of emotional stimuli, including facial expressions, non-verbal emotional sounds, or music [30]. This impairment is selective for negative emotions, and patients' ability for recognizing and reacting to positive emotions is often spared [31] or even disproportionately increased [32]. In addition to emotional recognition, patients with bvFTD have deficits in suppressing emotions, generating emotions, and perceiving self-conscious emotions [33]. Decreased gray matter volumes of the amygdala and AIC have been reported in bvFTD patients with impaired emotional recognition of facial expressions [34]. Amygdala atrophy, similar to AIC, occurs early in the course of bvFTD [35], and was consistently reported in our included studies.

The amygdala has reciprocal connections to the ventral striatum, as well as limbic and paralimbic brain regions [35], and has a central role in recognition of emotions, but also in reward processing, motivation, attention, learning and memory [36]. In addition, the amygdala along with the temporal pole, ventral striatum, and thalamus, is responsible for the SN functions that include providing the AIC with the information about socio-emotional valence of the external and internal world. The information from these different sources is integrated in the AIC, where the salience of the current state is determined/represented and passed on to more downstream regions [28].

Lack of empathy, i.e., impaired affective social cognition, is a core diagnostic feature of bvFTD [3] and is closely related to the deficits in emotional processing [37]. Empathy indicates an ability of identifying and sharing emotions and needs of other individuals [38]. Deficits in empathy can have a detrimental effect on the relationships of patients with their relatives and caregivers [39]. In addition, lack of empathy, and impaired social cognition in general, can result in disinhibition of socially inappropriate behaviors. More specifically, disinhibition might be a consequence of patients' inability to correctly identify social and emotional signals and their associated punishments/rewards, thereby neglecting the negative consequences of their own social acts [37]. Recent neuroimaging meta-analyses on healthy individuals have shown that empathy is consistently associated with activation of regions including the AIC, amygdala, ACC, thalamus, and lateral frontal regions [40, 41]. In addition, individual differences in socioemotional sensitivity have been shown to correlate with FC of the SN [42], and interestingly, socio-affective training aimed at improving empathy and compassion is associated with plasticity of the AIC [42]. Several neuroimaging studies on the neural correlates of empathy and social cognition in bvFTD patients have pointed out to abnormalities in the similar regions, such as the insula, thalamus, amygdala, inferior frontal gyrus, lateral orbitofrontal cortex, and medial frontal regions, including subcallosal and midcingulate cortex [32, 42-44]. Interestingly,

similar regions are involved in impaired socio-emotional dysfunctions of other neuropsychiatric disorders, such as autism spectrum disorder [45], conduct disorder [46], and schizophrenia [47].

Based on the 'simulation theory of empathy', humans use their own mind as a model to predict and understand the thoughts and feelings of others [26]. Therefore, and as self-awareness of affective states largely relies on interoception, i.e., awareness of internal bodily homeostatic state, it has been suggested that interoception has an important role in empathy [48]. These two closely related functions are presumed to be mediated by the AIC, where dual and corresponding mappings for subjective and empathetic feeling states are represented [38]. In line with this hypothesis, an fMRI study demonstrated that when subjects are interoceptively aware (attending to their heartbeats), they show a higher empathy-related brain activity in the AIC after observing emotionally valent facial expressions [48]. Patients with bvFTD display impaired interoception, as has been shown by their decreased performance in the heartbeat detection task [49], or their lower sensitivity to pain and temperature [50], which interestingly is associated with the atrophy of insula and fronto-temporal regions [49]. The lack of empathy in bvFTD patients could therefore be partially attributable to the impairments in interoception, which are due to AIC dysfunction.

According to our findings in the AIC, it is worthy to note that this convergent cluster was located more on the dorsal surface of the left AIC. This region, as suggested by previous studies and our functional decoding, is more involved in cognitive control and semantic functions [51], as opposed to the right and ventral AIC, which has a key role in socio-emotional processing [52]. Although we only include studies on bvFTD patients, this finding suggests that some studies might include bvFTD patients with concomitant language abnormalities or semantic variants of FTD. Nevertheless, the segregation of functions in the dorsal and ventral AIC is not as clear-cut and different functions of AIC have shown to converge on its dorsal surface [53]. In addition, our functional decoding analysis showed that the left dorsal AIC is more likely to be activated in interoception than in language functions, and as mentioned above,

interoception is a key component of empathy. Of note, previous neuroimaging meta-analyses of empathy have also shown activation of both left and right, as well as ventral and dorsal AIC in response to emotional stimuli [41].

#### **4.2. Limbic system abnormalities in bvFTD result in executive dysfunction and apathy**

The ACC, as the efferent hub of SN, coordinates initiation of appropriate behaviors in response to the states that are emotionally, socially, or homeostatically significant [28]. This function is mainly accomplished by switching the brain activity from the default mode network (DMN) to the central executive network (CEN) [54], which refers to the brain areas that are engaged during executive functions, i.e., cognitively demanding tasks that require sustained attention, including working memory, problem solving, planning, inhibiting, and development or implementation of strategies [55]. Executive dysfunction is a prominent symptom and a key diagnostic feature of bvFTD, which affects many domains of higher order brain functions, and contributes to development of apathy or inertia (see below) [56]. Meta-analytic studies have suggested that in healthy individuals, the frontoparietal and subcortical structures such as the dorsolateral prefrontal cortex, superior parietal lobules, dorsal ACC, thalamus, and striatum are involved in executive functions [55]. Accordingly, executive dysfunction in bvFTD patients is associated with atrophy of anterior cingulate and midcingulate gyri, medial frontal cortex, and lateral prefrontal cortex [57]. In the present meta-analysis, we found consistent abnormalities in the ACC and caudate nucleus in bvFTD patients. These regions were grouped together in the hierarchical clustering, and showed FC with each other, and other key regions of the CEN including the prefrontal cortex and superior parietal lobule. However, we found no consistent abnormality in the lateral frontal and parietal regions classically associated with executive functions. This finding suggests that in addition to the primary deficits in the ACC and striatum, executive dysfunction in bvFTD patients might be secondary to their inability to engage these lateral cortical regions due to dysfunction in the ACC and SN. Furthermore, as impairments in classical

executive functioning tasks occur later in the course of bvFTD [58], some patients may not have yet developed abnormalities in lateral regions of the CEN, making it less likely to be identified consistently across the literature.

Psychopathology of apathy or inertia involves impairments in motivation, initiation, and planning/execution [2]. Although all three components are dysfunctional in bvFTD patients, lack of motivation is the most prominent abnormality, which contributes to apathy [59]. Motivation refers to the ability of associating positive or negative affective signals with the value of actions and attempting to maximize value by seeking rewards and avoiding punishments [60]. In this context, abnormal reward processing can lead to a lack of motivation, both by reducing the inclination to perform and complete tasks and ability to comprehend the consequences of future actions [61]. Recent meta-analysis has shown that in healthy individuals, the striatum, insula, amygdala, thalamus, parahippocampal gyrus, and medial frontal regions such as the ACC are involved in reward processing [62]. We found convergent abnormalities in many of these reward-responsive regions including the left caudate, amygdala, paracingulate cortex, frontal medial cortex, and ACC. Interestingly, motivational deficits in bvFTD patients are associated with atrophy of the orbitofrontal cortex and ACC [63]. These findings suggest that lack of motivation in bvFTD patients occurs as a result of their decreased sensitivity to rewards and punishments, due to dysfunction of the ACC, orbitofrontal cortex, and striatum [61].

#### **4.3. The role of medial temporal lobe atrophy in amnestic features of bvFTD**

Classically, bvFTD has been mainly described as a predominantly behavioral disorder with less episodic memory impairment [3]. However, patients with bvFTD, like other dementia syndromes may have deficits in encoding and retrieval of autobiographical memories, comparable to that of AD [64]. It has been reported that impaired episodic memory functions in bvFTD patients is attributable to their executive dysfunction, i.e., their inability to properly monitor topics and events, check the relevance of incoming memories, and inhibit competing memories, due to

frontal lobe abnormalities [25]. Although executive dysfunction can be a contributing factor to amnesia, it has been suggested that similar to AD, amnestic bvFTD patients have atrophy or dysfunction of the hippocampus and other medial temporal lobe (MTL) structures [64, 65]. Similarly, we found convergent atrophy in the CA1 and dentate gyrus of the right anterior hippocampus. This finding is rather new than previous neuroimaging meta-analyses on bvFTD, which reported no convergent abnormalities in the MTL [6, 8, 66]. These findings, however, suggest that MTL atrophy and impaired episodic memory exist in bvFTD, and therefore intact memory function may not constitute a suitable differentiating factor between bvFTD and AD [67]. An alternative explanation might be that as both bvFTD and AD are often diagnosed using clinical diagnostic criteria that are not certain [68, 69], a portion of clinically-diagnosed bvFTD patients, when assessed histopathologically, may actually have AD pathology (e.g., 12 out of 63 patients [68]), or that frontotemporal lobar degeneration [68] and AD cover a spectrum of neurodegenerative disorders with some bvFTD patients also having underlying AD pathology (and vice versa) [70].

#### 4.4. Limitations and Future Directions

Our main limitation, which was in fact inherited from the included studies, was the heterogeneity of clinical samples, particularly regarding the severity of symptoms, histopathological subtypes, and molecular etiology of bvFTD. Several studies have suggested that distinct pathological or genetic subtypes of frontotemporal lobar degeneration [68] have different neuroanatomical correlates [71]. These subtypes are often difficult to determine, and therefore, very few studies had investigated them separately, preventing us from doing subgroup analyses on those specific subtypes. In addition, as most of the included studies had diagnosed bvFTD using the clinical criteria, it is possible that some of the patients had other disorders characterized by symptoms that can overlap with bvFTD, such as AD or other neuropsychiatric disorders [72].

Finally, two methodological limitation of our meta-analysis, which are common to all CBMA

methods, were that 1) pooling of findings was based on the peak coordinates of significant regions, which essentially ignores the volume and extent of clusters; 2) conventional ALE analysis could miss out biological heterogeneity.

As novel genetic and histopathological subtypes of bvFTD are introduced (C9ORF72 or MAPT expansion carriers or FTLD-tau and FTLD-TDP), curiosity about the specific clinical and neuroimaging characteristics of these phenotypes piques [71]. Although these phenotypes are appropriately diagnosed by present criteria of bvFTD, they do manifest with their individual group of symptoms (e.g., C9ORF72 expansion carriers mostly present with psychiatric symptoms) [73]. Looking further into the neurological and neuroimaging markers of genetically susceptible individuals (e.g. C9ORF72 expansion carriers) might give us invaluable insight into onset and pathophysiology of bvFTD. Therefore, the future individual and meta-analysis studies on each specific phenotype of bvFTD are a worthwhile endeavor to understand more about bvFTD.

## 5. Conclusion

We replicated some of the findings of previous meta-analyses on bvFTD in the frontomedial areas, AIC, and striatum. In addition, we identified a cluster of convergence in the amygdala and hippocampus, probably by virtue of a higher number of structural and functional experiments, as well as the increased meta-analytic power. On the other hand, we found no convergence in some of the regions commonly reported in previous meta-analyses, namely lateral frontal cortical areas and thalamus. The results of our study suggest that: 1) dysfunctions of the AIC and amygdala in bvFTD patients may impair their socio-emotional processing and may lead to disinhibition of socially inappropriate behaviors and a lack of empathy; 2) abnormalities of midline frontal regions, basal ganglia, and amygdala in patients with bvFTD may be responsible for their executive dysfunction, as well as apathy primarily through a lack of motivation; and 3)

hippocampal atrophy and amnestic symptoms may not suitably differentiate bvFTD and AD. In general, our results highlighted a crucial role of the salience network and subcortical regions in pathophysiology of bvFTD.

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## **DISCLOSURES**

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## Tables and Figures

**Table 1. (a)** The MNI coordinates of convergent regional abnormalities in bvFTD identified by ALE analysis on all experiments. bvFTD: Behavioral variant of Frontotemporal dementia, HC: Healthy controls, MNI: Montreal Neurological Institute atlas, VBM: Voxel-based morphometry, PET: 18F-fluorodeoxyglucose positron emission tomography, rs-fMRI: Resting-state functional magnetic resonance imaging, t-fMRI: Task-based functional magnetic resonance imaging, ACC: Anterior cingulate cortex, AIC: Anterior insular cortex

Comparison	Cluster	Region	Number of Voxels	MNI Coordinates (X, Y, Z)	P-Value
bvFTD<HC	i <sup>a</sup>	the right amygdala and hippocampus	240	24, -6, -14	p < 0.05, cFWE
	ii <sup>b</sup>	the left caudate and subcallosal cortex	534	-4, 12, -12	
	iii <sup>c</sup>	bilateral paracingulate gyrus and ACC	400	10, 34, 28	
	iv <sup>d</sup>	bilateral paracingulate gyrus extending to small portions of the medial orbitofrontal cortex	163	0, 36, -10	
	v <sup>e</sup>	the left AIC extending to frontal orbital cortex	173	-32, 22, 4	

- a. 17.8% of voxels located in CA1, 13.1% in centromedial amygdala, 11.1% in dentate gyrus, 11.4% in ventromedial amygdala, and 7.7% in basolateral amygdala. Convergence in this cluster was mostly driven by VBM experiments (87.8%).
- b. 5.8% voxels located in s24, 13.8% in area 25, 8.3% in area 33, 4.8 in area Fo2. Convergence in this cluster was driven VBM (54.6%), FDG-PET (28.5%), or both VBM and FDG-PET (16.8%).
- c. 14.1% of the volume is located in area 24c, 11.4% in area p32, 10.4% in area p24ab, and 2.6% in area 33. Convergence in this cluster was driven by VBM (53.8%), FDG-PET (33.6%), both VBM and rs-fMRI (7.3%), or both VBM and FDG-PET (5.1%) experiments.
- d. 52.5% of voxels located in area s32, 2.19% in area s24, 8.9% in area p24ab, and 3.6% in area p32. This cluster was mostly driven by VBM experiments (98.5%).

- e. 30.9% of voxels located in area Id6, 29.9% in area Id7, and 9.6% in area OP8. Convergence in this cluster was driven by VBM experiments (72.3%) and FDG-PET (27.2%).

**(b)** The MNI coordinates of convergent regional abnormalities in bvFTD identified by ALE analysis on modality experiments. bvFTD: Behavioral variant of Frontotemporal dementia, HC: Healthy controls, MNI: Montreal Neurological Institute atlas, VBM: Voxel-based morphometry, PET: 18F-fluorodeoxyglucose positron emission tomography, rs-fMRI: Resting-state functional magnetic resonance imaging, t-fMRI: Task-based functional magnetic resonance imaging, ACC: Anterior cingulate cortex, AIC: Anterior insular cortex

Comparison	Modality	Region	Number of Voxels	MNI	P-Value
				Coordinates (X, Y, Z)	
bvFTD<HC	VBM	the amygdala and hippocampus	304	24, -6, -14	p < 0.05, cFWE
		paracingulate gyrus and frontal medial cortex	203	0, 36, -10	
		AIC and frontal orbital cortex	100	-32, 22, 4	
bvFTD<HC	FDG-PET, rs-fMRI, t-fMRI <sup>a</sup>	left caudate and accumbens	276	-8, 10, 0	p < 0.05, cFWE
		paracingulate gyrus and ACC	296	10, 34, 26	
		rostral region of the ACC	156	4, 14, 34	

- a. Convergence in the significant clusters of functional analysis was mainly driven by FDG-PET (67.1%-100% contribution) and rs-fMRI experiments (11.1%-32.9%), while t-fMRI experiments had no contribution.

## **Figures' legends**

**Figure 1.** PRISMA flowchart of study selection. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

**Figure 2.** Convergence of brain imaging findings in bvFTD compared to healthy controls across all experiments (A), experiments reporting atrophy/hypoactivation (B), and experiments using functional (C, orange) or structural (C, green) modalities. The coordinates are in MNI space. Color bars represent Z values. ALE: activation likelihood estimation, bvFTD: behavioral-variant frontotemporal dementia, MNI: Montreal Neurological Institute.

**Figure 3.** The overlap of resting-state functional connectivity and meta-analytic connectivity maps of convergent regions in the all-effects ALE. The coordinates are in MNI space. MACM: meta-analytic connectivity map, RSFC: resting-state functional connectivity, Amyg: amygdala, Hipp: hippocampus, Caud: caudate nucleus, SCC: subcallosal cortex, PrCC: paracingulate cortex, FMC: frontomedial cortex, AIC: anterior insular cortex, ACC: anterior cingulate cortex, ALE: activation likelihood estimation, MNI: Montreal Neurological Institute.

**Figure 4.** Hierarchical clustering of convergent regions in the all-effects ALE. Below the pairwise functional connectivity matrix of the convergent regions is shown after Fischer's z-transformation and normalization to the maximum. Amyg: amygdala, Hipp: hippocampus, Caud: caudate nucleus, SCC: subcallosal cortex, PrCC: paracingulate cortex, FMC: frontomedial cortex, AIC: anterior insular cortex, ACC: anterior cingulate cortex, ALE: activation likelihood estimation, MNI: Montreal Neurological Institute

**Figure 5.** Functional decoding analysis of convergent regions in the all-effects ALE based on BrainMap behavioral domain categories and subcategories. The spider plot values are likelihood ratios. Amyg: amygdala, Hipp: hippocampus, Caud: caudate nucleus, SCC: subcallosal cortex, PrCC: paracingulate cortex, FMC: frontomedial cortex, AIC: anterior insular cortex, ACC: anterior cingulate cortex, ALE: activation likelihood estimation, MNI: Montreal Neurological Institute.

## Convergent regional brain abnormalities in behavioral variant frontotemporal dementia: a neuroimaging meta-analysis of 73 studies

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**Running title:** Neuroimaging Meta-analysis in bvFTD

**Keywords:** Behavioral Variant Frontotemporal Dementia; Activation Likelihood Estimation; Meta-Analytic Connectivity Modeling; Resting State Functional Connectivity; Hierarchical Clustering; Functional Decoding

## **Abstract**

**INTRODUCTION:** Numerous studies have reported brain alterations in behavioral variant frontotemporal dementia (bvFTD). However, they pointed to inconsistent findings.

**METHODS:** We used a meta-analytic approach to identify the convergent structural and functional brain abnormalities in bvFTD. Following current best-practice neuroimaging meta-analysis guidelines, we searched PubMed and Embase databases and performed reference tracking. Then, the coordinates of group comparisons between bvFTD and controls from 73 studies were extracted and tested for convergence using activation likelihood estimation.

**RESULTS:** We identified convergent abnormalities in the anterior cingulate cortices, anterior insula, amygdala, paracingulate, striatum, and hippocampus. Task-based and resting-state functional connectivity pointed to the networks that are connected to the obtained consistent regions. Functional decoding analyses suggested associated dysfunction of emotional processing, interoception, reward processing, higher-order cognitive functions, olfactory and gustatory perceptions in bvFTD.

**DISCUSSION:** Our findings highlighted a key role of the salience network and subcortical regions in the pathophysiology of bvFTD.

**Keywords:** Behavioral Variant Frontotemporal Dementia; Activation Likelihood Estimation; Meta-Analytic Connectivity Modeling; Resting State Functional Connectivity; Hierarchical Clustering; Functional Decoding.

## **1. INTRODUCTION**

Behavioral-variant frontotemporal dementia (bvFTD) is a neurodegenerative syndrome characterized by neurodegeneration in the frontal and anterior temporal lobes leading to insidious and progressive changes in behavior, personality, and social functions [1]. BvFTD is the most common frontotemporal dementia (FTD) syndrome and the second major cause of early-onset dementia after Alzheimer's disease (AD) [1]. Given the heterogeneous symptomology and gradual course of the disease, early detection of bvFTD is often abstruse and causes frustrating experiences for patients and relatives [2]. Accordingly, the current bvFTD diagnostic criteria has incorporated neuroimaging findings to improve the accuracy of clinical evaluation particularly in early stages [3].

The most identified structural and functional brain changes in early stages of bvFTD target a group of interconnected brain regions, so-called "salience network" (SN), which is associated with social-emotional processing [1]. However, individual neuroimaging studies in bvFTD point to divergent findings due to heterogeneous clinical samples, diversity of imaging modalities, flexible analyses, and statistical methods. Thus, quantitative assessment of neural abnormalities using neuroimaging meta-analysis is needed to overcome such divergence in the bvFTD literature [4, 5]. There are few prior bvFTD neuroimaging meta-analyses that indicated atrophy, hypoconnectivity, and hypometabolism in a wide number of brain regions covering the frontomedial cortex, basal ganglia, anterior insula, and the temporal cortex [6-8]. However, these previous meta-analyses were mostly unimodal (i.e., including only VBM experiments, FDG-PET, or resting-state fMRI (rs-fMRI)) [6-8], included a low number of patients, various selection criteria, and often used liberal statistical methods (e.g., FDR), which increases the opportunity for false positive results [9]. Moreover, previous meta-analyses have pooled only structural studies, highlighting the role of SN in bvFTD. Thus, a multimodal meta-analysis, including functional imaging results, might provide more information in pathophysiology of bvFTD.

In order to elucidate consensus structural and functional regional aberrations in bvFTD, we applied activation likelihood estimation (ALE), the most commonly applied algorithm among the coordinate-based meta-analysis (CBMA) methods, which assesses regional convergence between foci obtained from group comparison experiments [10]. Next, we located brain co-activation patterns using meta-analytic connectivity modeling (MACM) [11] and resting-state functional connectivity (RSFC) [12] to reveal networks connected to the meta-analytically obtained regions in task-based and resting-state experiments, respectively. Finally, we performed hierarchical clustering analysis based on the pairwise RSFC profile and functional decoding of the convergent clusters to reveal sub-networks between convergent regions and assess the mental functions associated with these regions, respectively. We assessed functional characteristics of the identified regions using the BrainMap dataset [13].

## 2. METHODS AND MATERIALS

The present large-scale CBMA was performed following the recently-developed, best-practice guidelines for neuroimaging meta-analyses [4, 5] and adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [14, 15]. The protocol for this study was pre-registered based on the International Prospective Register of Systematic Reviews (PROSPERO, code: CRD42020127902).

### 2.1. Search strategy, selection criteria, and quality appraisal

We performed a systematic literature search (up to May 2020) to identify structural and functional neuroimaging studies that compared bvFTD patients with their matched healthy controls (details are reported in the supplement). Studies were included if they (1) included clinically diagnosed bvFTD patients with no concurrent psychiatric diagnosis (e.g. major depressive disorder and bipolar mood disorder), other forms of dementia or neurological

symptoms, and no history of alcohol and substance abuse [3, 16]; (2) included at least six participants in either patient or healthy group; (3) used VBM, fMRI (resting-state or task based), and FDG-PET as the imaging modality; (4) reported the coordinates of between-group contrasts in a defined stochastic space (i.e., Montreal Neurological Institute [MNI] or Talairach); and (5) performed a whole-brain analysis. Thus, studies using seed-based FC, DTI, and cortical thickness methods were all excluded, as suggested previously [4, 5].

We used a 10-point checklist developed by Strakowski et al. [17] and employed by previous meta-analyses to assess individual study quality based on imaging methodology and clinical and demographic properties of the study [18-20]. The quality assessment score of included studies are reported in Table S1.

## **2.2. Activation likelihood estimation analysis**

The revised ALE algorithm was used to identify convergent patterns of brain alterations by showing a convergence of reported coordinates across experiments, which is higher than expected under a random spatial association [10]. The experiments were categorized by their effect direction (in-/decreases) and imaging modalities (see the supplement for details). Separate ALE meta-analyses were performed on four subsets of the experiments: (i) pooling all experiments together, (ii) experiments reporting decreases in activity/connectivity, metabolism or grey matter volume (Control > bvFTD), (iii) VBM experiments, and (iv) combination of functional imaging (FDG-PET, rs-fMRI, t-fMRI) experiments. The other sets of experiments, including experiments categorized based on diagnostic criteria, did not reach the minimum required number of experiments for sufficient power ( $\geq 17$ ) [9].

## **2.3. Meta-analytic connectivity modeling (MACM) and resting-state functional connectivity (RSFC)**

We investigated the task-based and task-free functional connectivity profiles of the obtained regions using MACM [11] and RSFC [12], respectively. MACM analysis uses task-based functional neuroimaging studies to meta-analytically identify regions that are co-activated across a range of different tasks with the seed regions, whereas RSFC identifies task-free FC patterns of the convergent meta-analytic clusters. A more detailed description of each analysis is available in the Supplement.

#### **2.4. Hierarchical clustering (HC) and functional decoding (FD)**

We performed HC analysis based on the pairwise RSFC profile of the identified regions to reveal the sub-networks associated with the convergent regions. Finally, we assessed the functional characteristics of the identified regions using the BrainMap dataset [13]. Detailed description of each analysis is available in the Supplement.

### **3. RESULTS**

#### **3.1. Experiments included in the meta-analysis**

After removing duplicate records, we screened a total number of 5,045 abstracts and included 73 studies in our meta-analysis (Figure 1, Table S1). The excluded studies and the reasons of exclusion are reported in Table S2. Of the 495 studies excluded by full-text screening from both electronic databases and reference checking, 124 were excluded because the subjects were not bvFTD patients, 97 were excluded because they did not report coordinates significantly different between two groups, and 78 were excluded due to using regions of interest (detailed reasons for exclusion are reported in Figure 1). Among the included papers, 27 studies were performed based on the FRONTIER open dataset and thus, their data were merged to minimize within-group effects [4]. In addition, eight other studies had partially overlapping samples, and they were pooled together as well. Finally, 31 independent experiments (out of 73 studies) comprising 1,672 bvFTD patients and 3,884 healthy participants were used for ALE analysis.

These experiments include VBM ( $N = 20$ ), t-fMRI ( $N = 1$ ), rs-fMRI ( $N = 2$ ) or FDG-PET ( $N = 12$ ). Of note, some experiments used more than one imaging modality; therefore, the collective number of experiments included in each imaging modality exceeds the number of total experiments. Decrease in functional/structural experiments (Controls > bvFTD) was observed more commonly ( $N = 28$ ) and only a few studies ( $N = 3$ ) reported increased functional/structural experiments (bvFTD > Controls).

### **3.2. Convergent regional abnormalities in bvFTD**

First, we assessed consistent structural and functional abnormalities by pooling all experiments ( $N = 31$ ) and identified five convergent clusters in the following regions ( $p < 0.05$ , cFWE): (i) the right amygdala and hippocampus; (ii) the left caudate and subcallosal cortex; (iii) bilateral paracingulate gyrus and anterior cingulate cortex (ACC); (iv) bilateral paracingulate gyrus extending to small portions of the medial orbitofrontal cortex; and (v) the left anterior insular cortex (AIC) extending to frontal orbital cortex (Figure 2A, Table 1a). Most of the included experiments reported "decrease" contrasts (Controls > bvFTD). So, performing ALE analysis on these experiments showed very similar convergent clusters ( $p < 0.05$ , cFWE) (Figure 2B).

Next, we performed separate ALE analyses for the imaging modality by categorizing the experiments to structural ( $N = 21$ ) and functional ( $N = 17$ ). The ALE analysis of structural (i.e., VBM) experiments revealed clusters of convergence in the amygdala and hippocampus, paracingulate gyrus and frontal medial cortex, as well as the AIC and frontal orbital cortex ( $p < 0.05$ , cFWE) (Table 1b, Figure 2C). The location of these clusters corresponded to the first, third, and fifth clusters of the all-experiments analysis respectively, but was smaller in size. Confining the analysis to the functional experiments (i.e., FDG-PET, rs-fMRI, and t-fMRI) demonstrated three significant clusters in the left caudate and accumbens, paracingulate gyrus and ACC and another more rostral region in the ACC ( $p < 0.05$ , cFWE). The last cluster, unlike

the other two, did not correspond to any of the regions identified in the all-experiments analysis (Figure 2C).

### **3.3. Connectivity patterns of the identified convergent regions**

The MACM and RSFC analyses pointed to the joint networks that are connected to the obtained clusters (Figure 3, Figures S1 and S2). The overlap of MACM and RSFC maps revealed significant task-based and task-free co-activation of the amygdala and hippocampus cluster with the striatum, thalamus, fusiform gyrus, inferior frontal gyrus, and midline frontal regions. MACM analysis demonstrated that the amygdala/hippocampus cluster has significant co-activation with the AIC. In addition, RSFC analysis showed additional task-free connectivity of amygdala/hippocampus cluster with the entorhinal cortex, superior and middle temporal gyri, precuneus, posterior cingulate cortex, and cerebellum.

The convergent cluster in the left caudate and subcallosal cortex was associated with the striatum, thalamus, AIC, midline frontal regions, posterior cingulate gyrus, and cerebellum in both MACM and RSFC analyses, but with the superior lateral occipital cortex, and middle temporal gyrus only in task-free analysis, and the left superior parietal lobule and parietal operculum only in task-based analysis.

The rostral paracingulate and frontal medial cortex cluster showed task-based coactivation and RSFC with the medial frontal regions, posterior cingulate cortex, precuneus, hippocampus, amygdala, and superior lateral occipital cortex, but was also functionally connected to the medial thalamus, AIC, Heschl's gyrus, and cerebellum only in RSFC analysis. Most of the significant regions for this cluster in the MACM analysis were also observed in the RSFC analysis.

The more caudal significant cluster in the paracingulate and ACC similarly functionally connected to the medial frontal regions, AIC, striatum, thalamus, middle and inferior frontal gyri, and posterior cingulate cortex in MACM and RSFC analyses, but additionally revealed RSFC

with the cerebellum, and meta-analytic co-activation with the superior parietal lobule and right angular gyrus.

The AIC cluster was functionally connected with the paracingulate gyrus and ACC, striatum, thalamus, middle and inferior frontal gyri, superior parietal lobule, and different regions within the cerebellum during both task and rest. In addition, the AIC showed only task-based functional connectivity with the precentral gyrus, fusiform gyrus, and superior parietal lobule, and RSFC with the temporal pole, Heschl's gyrus, intracalcarine cortex, and lingual gyrus. All these results were corrected for cFWE.

### **3.4. Hierarchical clustering of convergent findings**

To identify functionally coherent sub-networks of the identified consistent regions, we performed hierarchical clustering analysis based on their pairwise RSFC profile. In this analysis, at the first level, we identified two main sub-networks, namely the insula-amygda network, and the cingulo-striatal network including the ACC, paracingulate cortex, frontal medial cortex, subcallosal cortex, and striatum. The latter was grouped into two additional sub-networks at the second level: one including the two clusters located in the medial frontal lobe, and the other one including the convergent cluster in the striatum and subcallosal cortex (Figure 4).

### **3.5. Functional decoding of convergent clusters**

Our forward-inference functional decoding of the identified regions using the BrainMap database demonstrated their significant involvement in emotional processing, interoception, reward processing, higher-order cognitive functions, as well as olfactory and gustatory perception (Figure 5). More specifically, the amygdala/hippocampus cluster was activated in olfactory perception, processing of negative and positive emotions, and reward processing. The convergent cluster in the left caudate and subcallosal cortex was mostly associated with reward processing, gustatory perception, cognitive reasoning, and sexual interoception. Gustatory

perception and reward processing were also associated with activations in the rostral paracingulate gyrus / frontal medial cortex cluster. The more caudal paracingulate gyrus and the ACC cluster was more likely to be activated in cognitive reasoning and response to rewards. Finally, the AIC was associated with thermal interoception, processing of disgust, and language semantics. All these results were corrected for FDR.

#### **4. DISCUSSION**

We performed a large-scale CBMA on both structural and functional brain studies on bvFTD, nearly a decade after the revision of its diagnostic criteria and found consistent abnormalities in the five clusters including the AIC, ACC, paracingulate cortex (PrCC), subcallosal cortex, striatum, amygdala, and anterior hippocampus in patients with bvFTD compared to healthy subjects. These regions predominantly showed decreased gray matter volume, functional hypoactivation, or dysconnectivity, to various degrees in each region. While the abnormalities in the striatum were mainly functional, structural abnormalities were more predominant in the AIC, amygdala, and anterior hippocampus, and midline frontal regions were both functionally and structurally impaired. In addition, we used MACM and RSFC analyses to characterize the connectivity pattern of the convergent regions and observed significant co-activation of them with each other, and with additional brain regions including the thalamus, lateral prefrontal cortex, and association cortices in the parietal lobe. Next, using hierarchical clustering of the convergent regions, we classified them into two main groups: one including the AIC, amygdala, and hippocampus, and the other one including the midline frontal areas and striatum. Moreover, functional decoding analysis showed involvement of the former first set of regions in emotional processing, and of the latter in reward processing and higher-order cognitive functions.

##### **4.1. The key role of the salience network in bvFTD**

The cortical layer 5b of AIC and pregenual ACC (pgACC) contains a specialized type of large spindle-shaped projection neurons called von Economo neurons (VEN), which are presumed to be involved in social cognition and self-awareness [21]. The number of these neurons in the AIC and pgACC is significantly depleted in patients with bvFTD [22-24], parallel to clinical severity of bvFTD, and even in the absence of gross atrophy of these regions [21]. Accordingly, histopathological and imaging studies have suggested that the AIC and pgACC are among the earliest atrophied regions in bvFTD [25]. These regions are the key hubs of the SN, which guides behavior in response to the perceived salience of current external/internal events, i.e., their significance for the survival of the individuals [24]. In this network, the AIC and pgACC play distinct, but interdependent roles, acting as afferent (“sensory”) and efferent (“motor”) hubs of the SN, respectively. More specifically, the AIC detects and represents subjective emotional, homeostatic, social, and motivational salience of the immediate environmental or bodily states [26, 27], and the ACC initiates goal-directed behaviors in response to these salient stimuli [28]. Several studies have reported decreased FC within the SN in patients with bvFTD [29]. It is well-documented that the main hubs of the SN can lead to the main characteristic symptoms of bvFTD, including impaired emotional processing and social cognition, disinhibition, executive dysfunction, and apathy.

Impaired emotional recognition is a common symptom in bvFTD and has been reported for different types of emotional stimuli, including facial expressions, non-verbal emotional sounds, or music [30]. This impairment is selective for negative emotions, and patients' ability for recognizing and reacting to positive emotions is often spared [31] or even disproportionately increased [32]. In addition to emotional recognition, patients with bvFTD have deficits in suppressing emotions, generating emotions, and perceiving self-conscious emotions [33]. Decreased gray matter volumes of the amygdala and AIC have been reported in bvFTD patients with impaired emotional recognition of facial expressions [34]. Amygdala atrophy, similar to AIC, occurs early in the course of bvFTD [35], and was consistently reported in our included studies.

The amygdala has reciprocal connections to the ventral striatum, as well as limbic and paralimbic brain regions [35], and has a central role in recognition of emotions, but also in reward processing, motivation, attention, learning and memory [36]. In addition, the amygdala along with the temporal pole, ventral striatum, and thalamus, is responsible for the SN functions that include providing the AIC with the information about socio-emotional valence of the external and internal world. The information from these different sources is integrated in the AIC, where the salience of the current state is determined/represented and passed on to more downstream regions [28].

Lack of empathy, i.e., impaired affective social cognition, is a core diagnostic feature of bvFTD [3] and is closely related to the deficits in emotional processing [37]. Empathy indicates an ability of identifying and sharing emotions and needs of other individuals [38]. Deficits in empathy can have a detrimental effect on the relationships of patients with their relatives and caregivers [39]. In addition, lack of empathy, and impaired social cognition in general, can result in disinhibition of socially inappropriate behaviors. More specifically, disinhibition might be a consequence of patients' inability to correctly identify social and emotional signals and their associated punishments/rewards, thereby neglecting the negative consequences of their own social acts [37]. Recent neuroimaging meta-analyses on healthy individuals have shown that empathy is consistently associated with activation of regions including the AIC, amygdala, ACC, thalamus, and lateral frontal regions [40, 41]. In addition, individual differences in socioemotional sensitivity have been shown to correlate with FC of the SN [42], and interestingly, socio-affective training aimed at improving empathy and compassion is associated with plasticity of the AIC [42]. Several neuroimaging studies on the neural correlates of empathy and social cognition in bvFTD patients have pointed out to abnormalities in the similar regions, such as the insula, thalamus, amygdala, inferior frontal gyrus, lateral orbitofrontal cortex, and medial frontal regions, including subcallosal and midcingulate cortex [32, 42-44]. Interestingly,

similar regions are involved in impaired socio-emotional dysfunctions of other neuropsychiatric disorders, such as autism spectrum disorder [45], conduct disorder [46], and schizophrenia [47].

Based on the 'simulation theory of empathy', humans use their own mind as a model to predict and understand the thoughts and feelings of others [26]. Therefore, and as self-awareness of affective states largely relies on interoception, i.e., awareness of internal bodily homeostatic state, it has been suggested that interoception has an important role in empathy [48]. These two closely related functions are presumed to be mediated by the AIC, where dual and corresponding mappings for subjective and empathetic feeling states are represented [38]. In line with this hypothesis, an fMRI study demonstrated that when subjects are interoceptively aware (attending to their heartbeats), they show a higher empathy-related brain activity in the AIC after observing emotionally valent facial expressions [48]. Patients with bvFTD display impaired interoception, as has been shown by their decreased performance in the heartbeat detection task [49], or their lower sensitivity to pain and temperature [50], which interestingly is associated with the atrophy of insula and fronto-temporal regions [49]. The lack of empathy in bvFTD patients could therefore be partially attributable to the impairments in interoception, which are due to AIC dysfunction.

According to our findings in the AIC, it is worthy to note that this convergent cluster was located more on the dorsal surface of the left AIC. This region, as suggested by previous studies and our functional decoding, is more involved in cognitive control and semantic functions [51], as opposed to the right and ventral AIC, which has a key role in socio-emotional processing [52]. Although we only include studies on bvFTD patients, this finding suggests that some studies might include bvFTD patients with concomitant language abnormalities or semantic variants of FTD. Nevertheless, the segregation of functions in the dorsal and ventral AIC is not as clear-cut and different functions of AIC have shown to converge on its dorsal surface [53]. In addition, our functional decoding analysis showed that the left dorsal AIC is more likely to be activated in interoception than in language functions, and as mentioned above,

interoception is a key component of empathy. Of note, previous neuroimaging meta-analyses of empathy have also shown activation of both left and right, as well as ventral and dorsal AIC in response to emotional stimuli [41].

#### **4.2. Limbic system abnormalities in bvFTD result in executive dysfunction and apathy**

The ACC, as the efferent hub of SN, coordinates initiation of appropriate behaviors in response to the states that are emotionally, socially, or homeostatically significant [28]. This function is mainly accomplished by switching the brain activity from the default mode network (DMN) to the central executive network (CEN) [54], which refers to the brain areas that are engaged during executive functions, i.e., cognitively demanding tasks that require sustained attention, including working memory, problem solving, planning, inhibiting, and development or implementation of strategies [55]. Executive dysfunction is a prominent symptom and a key diagnostic feature of bvFTD, which affects many domains of higher order brain functions, and contributes to development of apathy or inertia (see below) [56]. Meta-analytic studies have suggested that in healthy individuals, the frontoparietal and subcortical structures such as the dorsolateral prefrontal cortex, superior parietal lobules, dorsal ACC, thalamus, and striatum are involved in executive functions [55]. Accordingly, executive dysfunction in bvFTD patients is associated with atrophy of anterior cingulate and midcingulate gyri, medial frontal cortex, and lateral prefrontal cortex [57]. In the present meta-analysis, we found consistent abnormalities in the ACC and caudate nucleus in bvFTD patients. These regions were grouped together in the hierarchical clustering, and showed FC with each other, and other key regions of the CEN including the prefrontal cortex and superior parietal lobule. However, we found no consistent abnormality in the lateral frontal and parietal regions classically associated with executive functions. This finding suggests that in addition to the primary deficits in the ACC and striatum, executive dysfunction in bvFTD patients might be secondary to their inability to engage these lateral cortical regions due to dysfunction in the ACC and SN. Furthermore, as impairments in classical

executive functioning tasks occur later in the course of bvFTD [58], some patients may not have yet developed abnormalities in lateral regions of the CEN, making it less likely to be identified consistently across the literature.

Psychopathology of apathy or inertia involves impairments in motivation, initiation, and planning/execution [2]. Although all three components are dysfunctional in bvFTD patients, lack of motivation is the most prominent abnormality, which contributes to apathy [59]. Motivation refers to the ability of associating positive or negative affective signals with the value of actions and attempting to maximize value by seeking rewards and avoiding punishments [60]. In this context, abnormal reward processing can lead to a lack of motivation, both by reducing the inclination to perform and complete tasks and ability to comprehend the consequences of future actions [61]. Recent meta-analysis has shown that in healthy individuals, the striatum, insula, amygdala, thalamus, parahippocampal gyrus, and medial frontal regions such as the ACC are involved in reward processing [62]. We found convergent abnormalities in many of these reward-responsive regions including the left caudate, amygdala, paracingulate cortex, frontal medial cortex, and ACC. Interestingly, motivational deficits in bvFTD patients are associated with atrophy of the orbitofrontal cortex and ACC [63]. These findings suggest that lack of motivation in bvFTD patients occurs as a result of their decreased sensitivity to rewards and punishments, due to dysfunction of the ACC, orbitofrontal cortex, and striatum [61].

#### **4.3. The role of medial temporal lobe atrophy in amnestic features of bvFTD**

Classically, bvFTD has been mainly described as a predominantly behavioral disorder with less episodic memory impairment [3]. However, patients with bvFTD, like other dementia syndromes may have deficits in encoding and retrieval of autobiographical memories, comparable to that of AD [64]. It has been reported that impaired episodic memory functions in bvFTD patients is attributable to their executive dysfunction, i.e., their inability to properly monitor topics and events, check the relevance of incoming memories, and inhibit competing memories, due to

frontal lobe abnormalities [25]. Although executive dysfunction can be a contributing factor to amnesia, it has been suggested that similar to AD, amnestic bvFTD patients have atrophy or dysfunction of the hippocampus and other medial temporal lobe (MTL) structures [64, 65]. Similarly, we found convergent atrophy in the CA1 and dentate gyrus of the right anterior hippocampus. This finding is rather new than previous neuroimaging meta-analyses on bvFTD, which reported no convergent abnormalities in the MTL [6, 8, 66]. These findings, however, suggest that MTL atrophy and impaired episodic memory exist in bvFTD, and therefore intact memory function may not constitute a suitable differentiating factor between bvFTD and AD [67]. An alternative explanation might be that as both bvFTD and AD are often diagnosed using clinical diagnostic criteria that are not certain [68, 69], a portion of clinically-diagnosed bvFTD patients, when assessed histopathologically, may actually have AD pathology (e.g., 12 out of 63 patients [68]), or that frontotemporal lobar degeneration [68] and AD cover a spectrum of neurodegenerative disorders with some bvFTD patients also having underlying AD pathology (and vice versa) [70].

#### **4.4. Limitations and Future Directions**

Our main limitation, which was in fact inherited from the included studies, was the heterogeneity of clinical samples, particularly regarding the severity of symptoms, histopathological subtypes, and molecular etiology of bvFTD. Several studies have suggested that distinct pathological or genetic subtypes of frontotemporal lobar degeneration [68] have different neuroanatomical correlates [71]. These subtypes are often difficult to determine, and therefore, very few studies had investigated them separately, preventing us from doing subgroup analyses on those specific subtypes. In addition, as most of the included studies had diagnosed bvFTD using the clinical criteria, it is possible that some of the patients had other disorders characterized by symptoms that can overlap with bvFTD, such as AD or other neuropsychiatric disorders [72]. Finally, two methodological limitation of our meta-analysis, which are common to all CBMA

methods, were that 1) pooling of findings was based on the peak coordinates of significant regions, which essentially ignores the volume and extent of clusters; 2) conventional ALE analysis could miss out biological heterogeneity.

As novel genetic and histopathological subtypes of bvFTD are introduced (C9ORF72 or MAPT expansion carriers or FTLD-tau and FTLD-TDP), curiosity about the specific clinical and neuroimaging characteristics of these phenotypes piques [71]. Although these phenotypes are appropriately diagnosed by present criteria of bvFTD, they do manifest with their individual group of symptoms (e.g., C9ORF72 expansion carriers mostly present with psychiatric symptoms) [73]. Looking further into the neurological and neuroimaging markers of genetically susceptible individuals (e.g. C9ORF72 expansion carriers) might give us invaluable insight into onset and pathophysiology of bvFTD. Therefore, the future individual and meta-analysis studies on each specific phenotype of bvFTD are a worthwhile endeavor to understand more about bvFTD.

## 5. Conclusion

We replicated some of the findings of previous meta-analyses on bvFTD in the frontomedial areas, AIC, and striatum. In addition, we identified a cluster of convergence in the amygdala and hippocampus, probably by virtue of a higher number of structural and functional experiments, as well as the increased meta-analytic power. On the other hand, we found no convergence in some of the regions commonly reported in previous meta-analyses, namely lateral frontal cortical areas and thalamus. The results of our study suggest that: 1) dysfunctions of the AIC and amygdala in bvFTD patients may impair their socio-emotional processing and may lead to disinhibition of socially inappropriate behaviors and a lack of empathy; 2) abnormalities of midline frontal regions, basal ganglia, and amygdala in patients with bvFTD may be responsible for their executive dysfunction, as well as apathy primarily through a lack of motivation; and 3)

hippocampal atrophy and amnestic symptoms may not suitably differentiate bvFTD and AD. In general, our results highlighted a crucial role of the salience network and subcortical regions in pathophysiology of bvFTD.

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## **DISCLOSURES**

None of the authors report financial interests or potential conflicts of interest.

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## Tables and Figures

**Table 1. (a)** The MNI coordinates of convergent regional abnormalities in bvFTD identified by ALE analysis on all experiments. bvFTD: Behavioral variant of Frontotemporal dementia, HC: Healthy controls, MNI: Montreal Neurological Institute atlas, VBM: Voxel-based morphometry, PET: 18F-fluorodeoxyglucose positron emission tomography, rs-fMRI: Resting-state functional magnetic resonance imaging, t-fMRI: Task-based functional magnetic resonance imaging, ACC: Anterior cingulate cortex, AIC: Anterior insular cortex

Comparison	Cluster	Region	Number of Voxels	MNI Coordinates (X, Y, Z)	P-Value
bvFTD<HC	i <sup>a</sup>	the right amygdala and hippocampus	240	24, -6, -14	p < 0.05, cFWE
	ii <sup>b</sup>	the left caudate and subcallosal cortex	534	-4, 12, -12	
	iii <sup>c</sup>	bilateral paracingulate gyrus and ACC	400	10, 34, 28	
	iv <sup>d</sup>	bilateral paracingulate gyrus extending to small portions of the medial orbitofrontal cortex	163	0, 36, -10	
	v <sup>e</sup>	the left AIC extending to frontal orbital cortex	173	-32, 22, 4	

- a. 17.8% of voxels located in CA1, 13.1% in centromedial amygdala, 11.1% in dentate gyrus, 11.4% in ventromedial amygdala, and 7.7% in basolateral amygdala. Convergence in this cluster was mostly driven by VBM experiments (87.8%).
- b. 5.8% voxels located in s24, 13.8% in area 25, 8.3% in area 33, 4.8 in area Fo2. Convergence in this cluster was driven VBM (54.6%), FDG-PET (28.5%), or both VBM and FDG-PET (16.8%).
- c. 14.1% of the volume is located in area 24c, 11.4% in area p32, 10.4% in area p24ab, and 2.6% in area 33. Convergence in this cluster was driven by VBM (53.8%), FDG-PET (33.6%), both VBM and rs-fMRI (7.3%), or both VBM and FDG-PET (5.1%) experiments.
- d. 52.5% of voxels located in area s32, 2.19% in area s24, 8.9% in area p24ab, and 3.6% in area p32. This cluster was mostly driven by VBM experiments (98.5%).

- e. 30.9% of voxels located in area Id6, 29.9% in area Id7, and 9.6% in area OP8. Convergence in this cluster was driven by VBM experiments (72.3%) and FDG-PET (27.2%).

**(b)** The MNI coordinates of convergent regional abnormalities in bvFTD identified by ALE analysis on modality experiments. bvFTD: Behavioral variant of Frontotemporal dementia, HC: Healthy controls, MNI: Montreal Neurological Institute atlas, VBM: Voxel-based morphometry, PET: 18F-fluorodeoxyglucose positron emission tomography, rs-fMRI: Resting-state functional magnetic resonance imaging, t-fMRI: Task-based functional magnetic resonance imaging, ACC: Anterior cingulate cortex, AIC: Anterior insular cortex

Comparison	Modality	Region	Number of Voxels	MNI	P-Value
				Coordinates (X, Y, Z)	
bvFTD<HC	VBM	the amygdala and hippocampus	304	24, -6, -14	p < 0.05, cFWE
		paracingulate gyrus and frontal medial cortex	203	0, 36, -10	
		AIC and frontal orbital cortex	100	-32, 22, 4	
bvFTD<HC	FDG-PET, rs-fMRI, t-fMRI <sup>a</sup>	left caudate and accumbens	276	-8, 10, 0	p < 0.05, cFWE
		paracingulate gyrus and ACC	296	10, 34, 26	
		rostral region of the ACC	156	4, 14, 34	

- a. Convergence in the significant clusters of functional analysis was mainly driven by FDG-PET (67.1%-100% contribution) and rs-fMRI experiments (11.1%-32.9%), while t-fMRI experiments had no contribution.

## **Figures' legends**

**Figure 1.** PRISMA flowchart of study selection. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

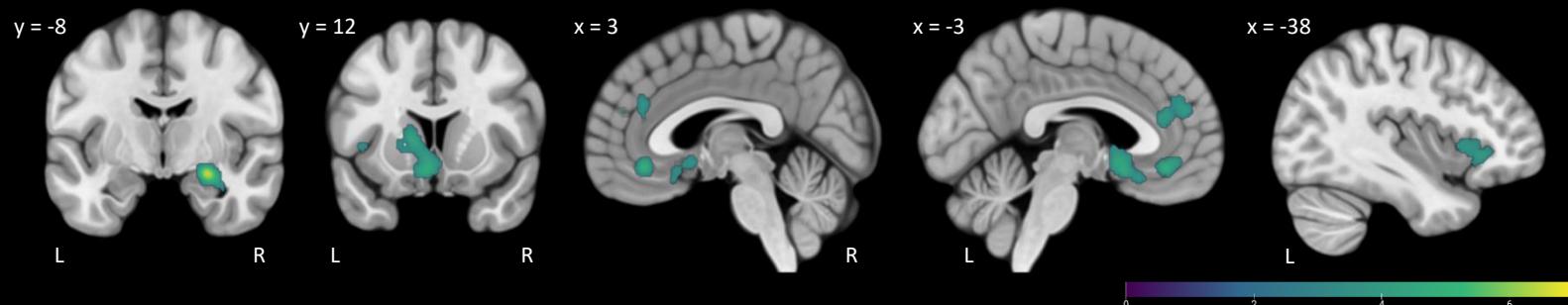
**Figure 2.** Convergence of brain imaging findings in bvFTD compared to healthy controls across all experiments (A), experiments reporting atrophy/hypoactivation (B), and experiments using functional (C, orange) or structural (C, green) modalities. The coordinates are in MNI space. Color bars represent Z values. ALE: activation likelihood estimation, bvFTD: behavioral-variant frontotemporal dementia, MNI: Montreal Neurological Institute.

**Figure 3.** The overlap of resting-state functional connectivity and meta-analytic connectivity maps of convergent regions in the all-effects ALE. The coordinates are in MNI space. MACM: meta-analytic connectivity map, RSFC: resting-state functional connectivity, Amyg: amygdala, Hipp: hippocampus, Caud: caudate nucleus, SCC: subcallosal cortex, PrCC: paracingulate cortex, FMC: frontomedial cortex, AIC: anterior insular cortex, ACC: anterior cingulate cortex, ALE: activation likelihood estimation, MNI: Montreal Neurological Institute.

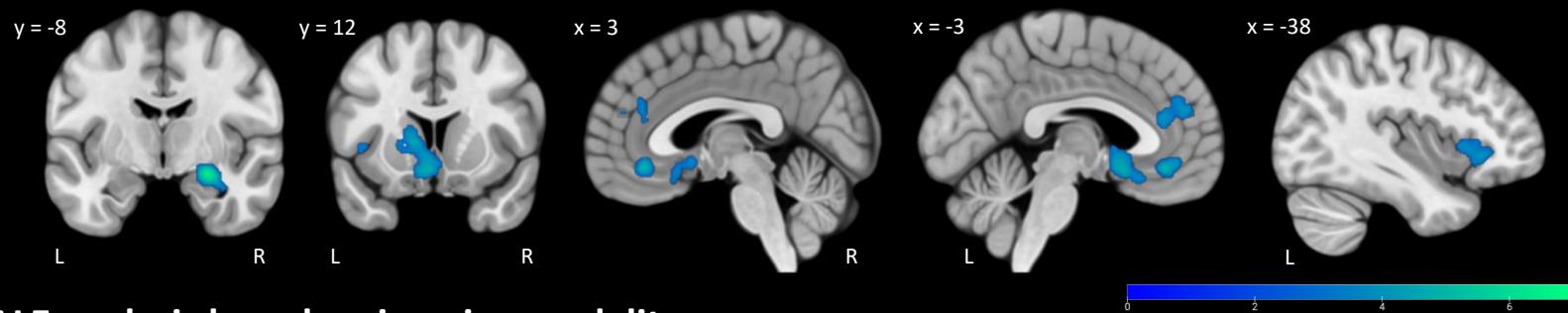
**Figure 4.** Hierarchical clustering of convergent regions in the all-effects ALE. Below the pairwise functional connectivity matrix of the convergent regions is shown after Fischer's z-transformation and normalization to the maximum. Amyg: amygdala, Hipp: hippocampus, Caud: caudate nucleus, SCC: subcallosal cortex, PrCC: paracingulate cortex, FMC: frontomedial cortex, AIC: anterior insular cortex, ACC: anterior cingulate cortex, ALE: activation likelihood estimation, MNI: Montreal Neurological Institute

**Figure 5.** Functional decoding analysis of convergent regions in the all-effects ALE based on BrainMap behavioral domain categories and subcategories. The spider plot values are likelihood ratios. Amyg: amygdala, Hipp: hippocampus, Caud: caudate nucleus, SCC: subcallosal cortex, PrCC: paracingulate cortex, FMC: frontomedial cortex, AIC: anterior insular cortex, ACC: anterior cingulate cortex, ALE: activation likelihood estimation, MNI: Montreal Neurological Institute.

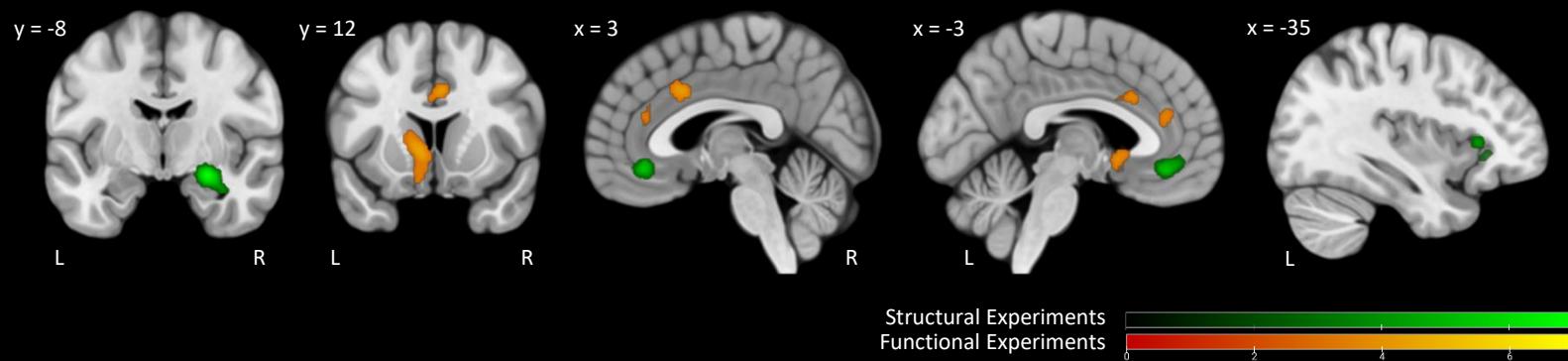
### A. ALE analysis based on differences between bvFTD and Controls



### B. ALE analysis based on group contrast (bvFTD < Controls)



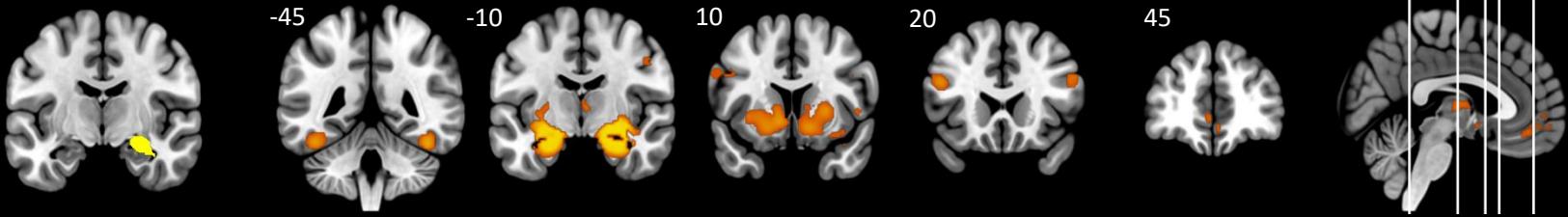
### C. ALE analysis based on imaging modality



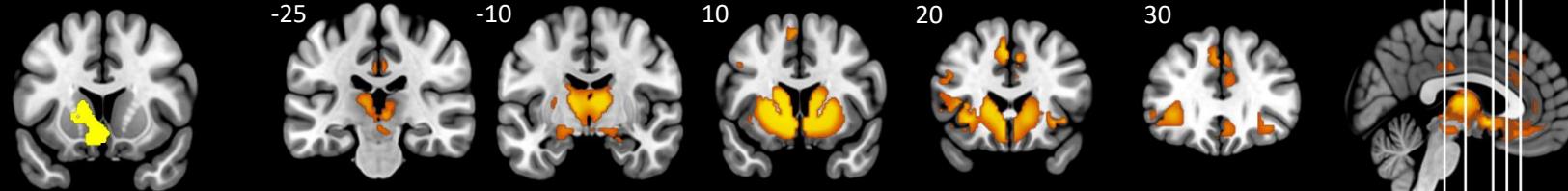
**Seed**

**MACM and RSFC overlap**

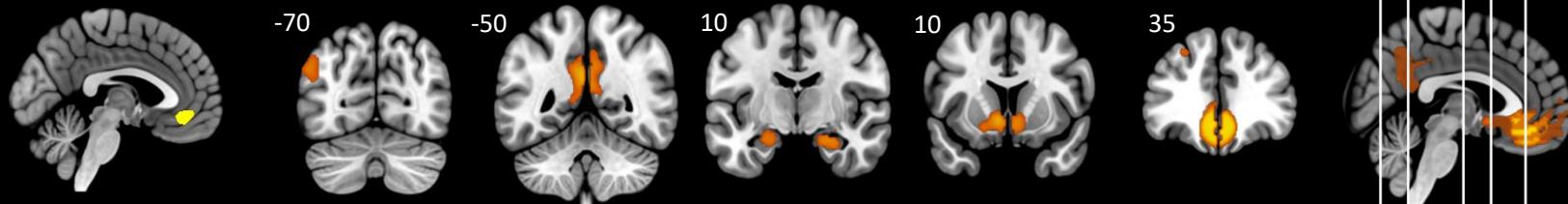
Amyg/Hipp



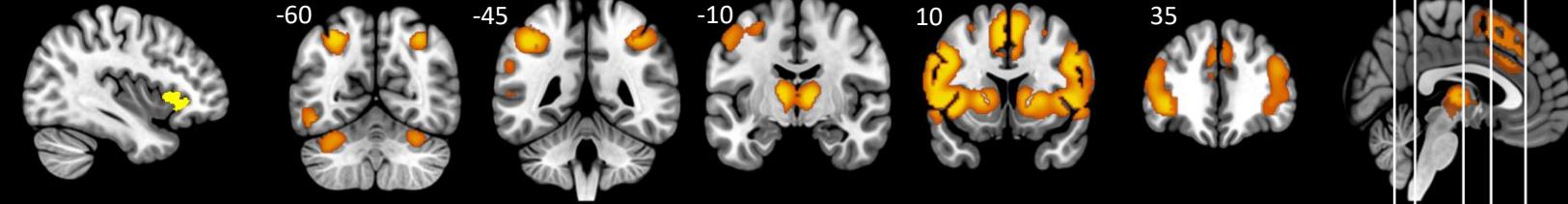
Caud/SCC



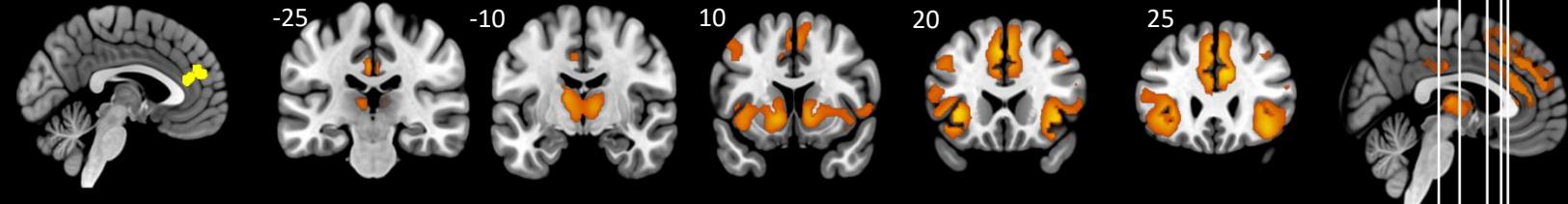
PrCC / FMC



AIC



PrCC/ACC



L

R



Figure 4

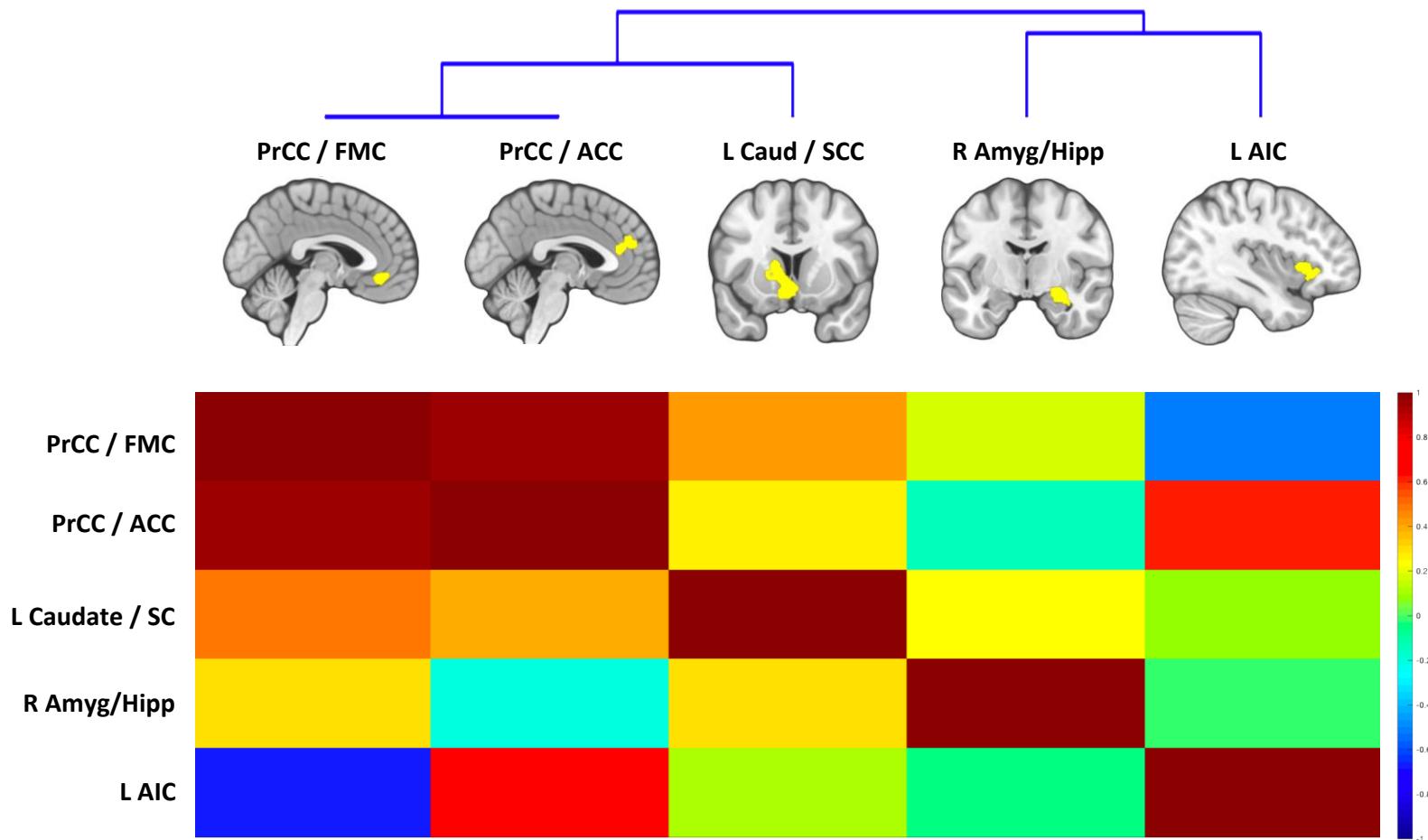


Figure 5

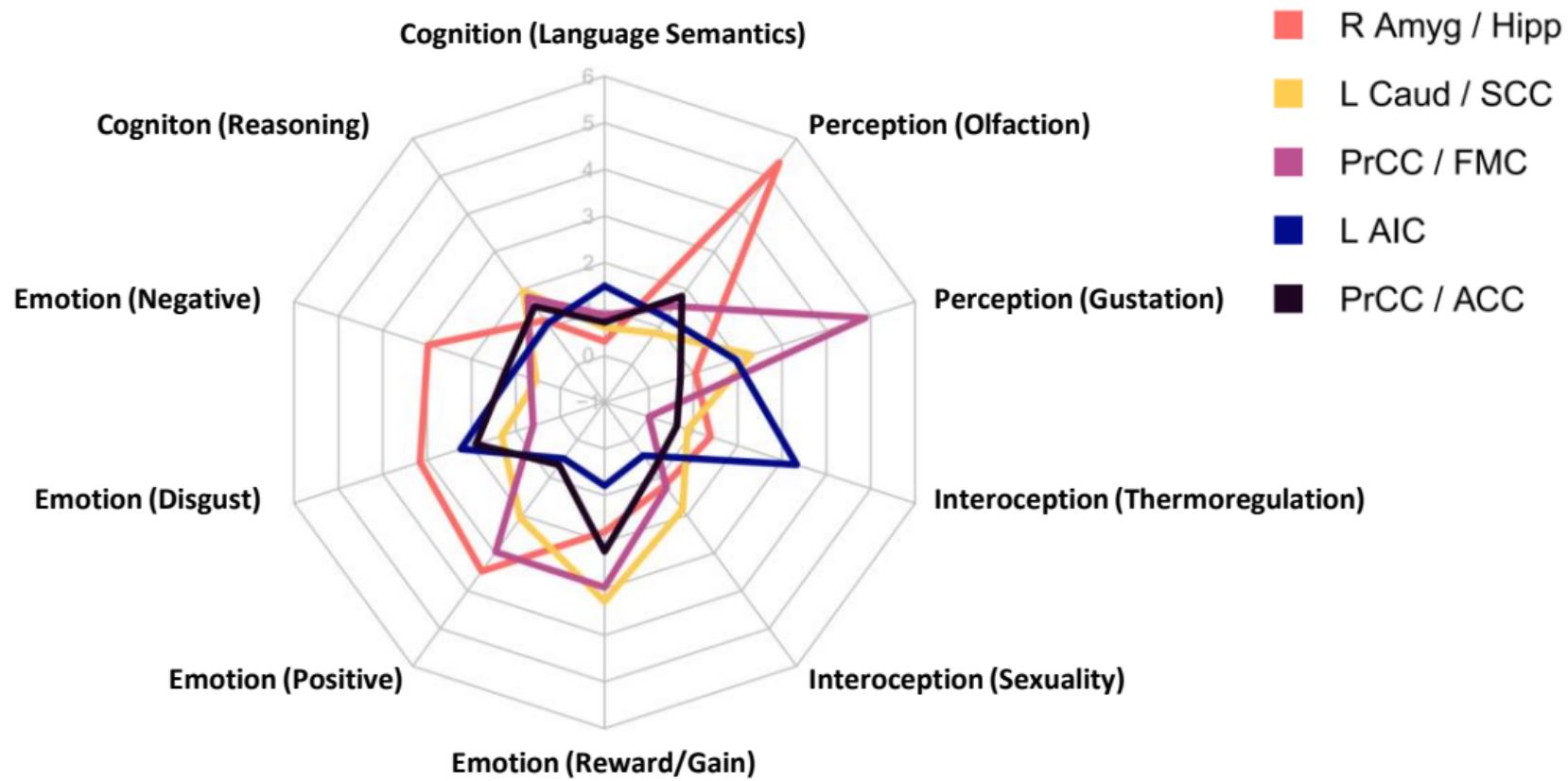
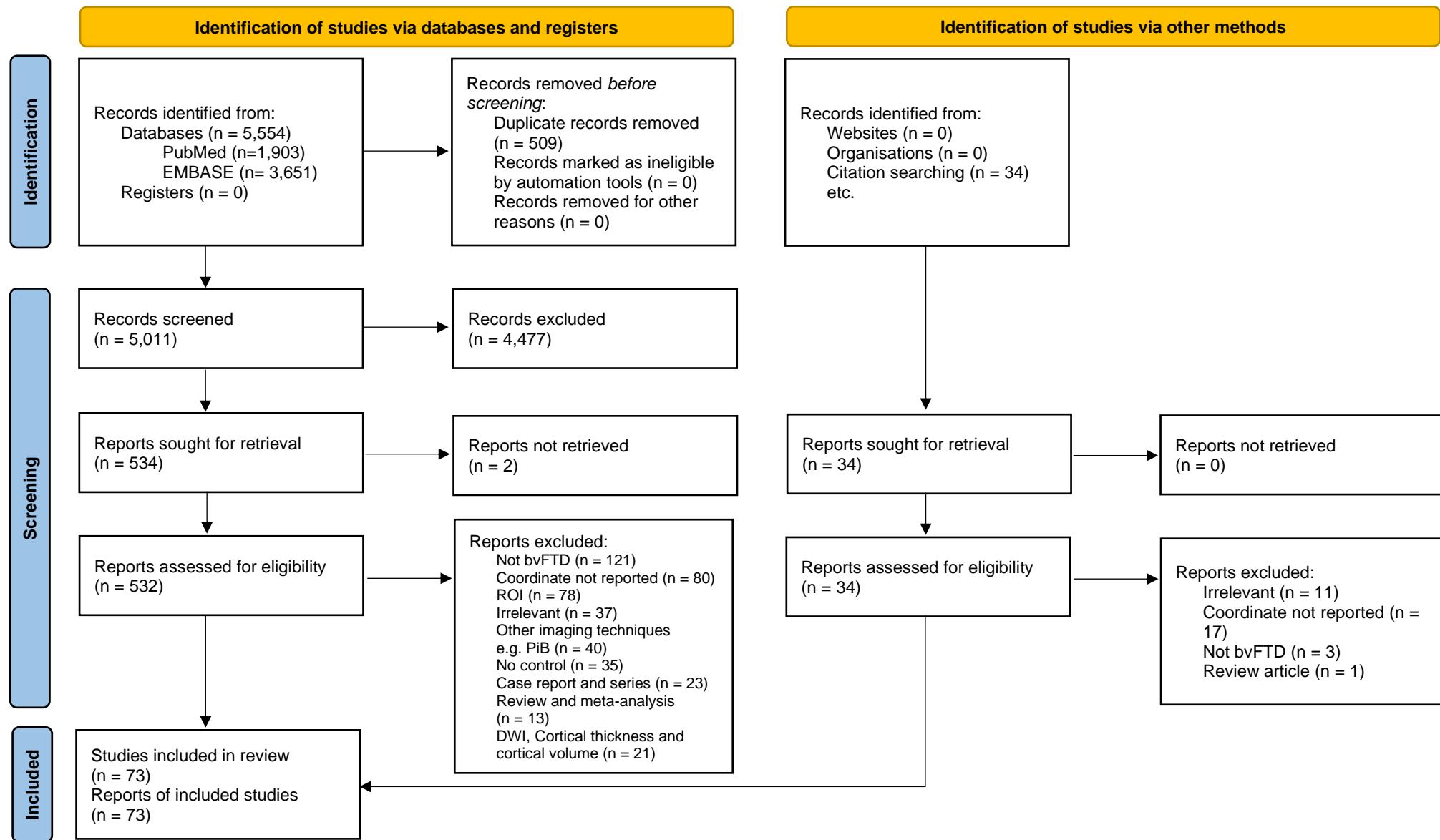


Figure 1

**PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources**



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: <http://www.prisma-statement.org/>

## **Research in Context**

**Systematic review:** Following the best-practice guideline, this large-scale meta-analysis we searched PubMed and Embase databases and performed reference tracking to identify convergent regional abnormality across structural and functional neuroimaging studies on behavioral-variant frontotemporal dementia (bvFTD).

**Interpretation:** Our findings found consistent regional brain abnormality in the salience network and subcortical regions in bvFTD.

**Future directions:** The future individual and meta-analysis studies on each specific phenotype of bvFTD are a worthwhile endeavor to understand more about the pathophysiology of bvFTD.



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