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Research report

Conceptualizing neuropsychiatric diseases with multimodal data-driven meta-analyses – The case of behavioral variant frontotemporal dementia

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ABSTRACT

Introduction: Uniform coordinate systems in neuroimaging research have enabled comprehensive systematic and quantitative meta-analyses. Such approaches are particularly relevant for neuropsychiatric diseases, the understanding of their symptoms, prediction and treatment. Behavioral variant frontotemporal dementia (bvFTD), a common neurodegenerative syndrome, is characterized by deep alterations in behavior and personality. Investigating this 'nexopathy' elucidates the healthy social and emotional brain.
Methods: Here, we combine three multimodal meta-analyses approaches – anatomical and activation likelihood estimates and behavioral domain profiles – to identify neural correlates of bvFTD in 417 patients and 406 control subjects and to extract mental functions associated with this disease by meta-analyzing functional activation studies in the comprehensive probabilistic functional brain atlas of the BrainMap database.
Results: The analyses identify the frontomedian cortex, basal ganglia, anterior insulae and thalamus as most relevant hubs, with a regional dissociation between atrophy and hypometabolism. Neural networks affected by bvFTD were associated with emotion and reward processing, empathy and executive functions (mainly inhibition), suggesting these functions as core domains affected by the disease and finally leading to its clinical

Abbreviations: AcLE, activation likelihood estimate; AnLE, anatomical likelihood estimate; bvFTD, behavioral variant frontotemporal dementia; DSM, Diagnostic and Statistical Manual of Mental Disorders; FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography; FTLD, frontotemporal lobar degeneration; MMSE, Mini Mental State Examination; MNI, Montreal Neurological Institute; MRI, magnetic resonance imaging; ToM, theory of mind.

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symptoms. In contrast, changes in theory of mind or mentalizing abilities seem to be secondary phenomena of executive dysfunctions.

Conclusions: The study creates a novel conceptual framework to understand neuropsychiatric diseases by powerful data-driven meta-analytic approaches that shall be extended to the whole neuropsychiatric spectrum in the future.

1. Introduction

Neurodegenerative disorders are a major public health problem. Frontotemporal lobar degeneration (FTLD) is the second most common diagnosis of dementia in individuals younger than 65 years (Johnson et al., 2005). Clinical criteria divide FTLD into three major subtypes: two subtypes affecting language functions, semantic dementia and progressive nonfluent aphasia, and the behavioral variant frontotemporal dementia (bvFTD) (Neary et al., 1998). bvFTD is the most common subtype and characterized by deep alterations in behavior and personality, namely decline in social interpersonal conduct, impairment in regulation of personal conduct, emotional blunting, and loss of insight ('diagnostic core features' according to Neary et al., 1998).

Recently, an international consortium revised bvFTD's diagnostic criteria by focusing on clinical symptoms in histopathologically confirmed cases (Piguet, Hornberger, Mioshi, & Hodges, 2011; Rascovsky et al., 2011). Now, 'possible' bvFTD requires three of six clinically discriminating features: disinhibition, apathy/inertia, loss of sympathy/empathy, perseverative/stereotyped/compulsive/ritualistic behaviors, hyperorality/dietary changes and dysexecutive neuropsychological profile. Interestingly, the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) has included also a decline in social cognition to the criteria (American Psychiatric Association, 2013). 'Probable' bvFTD adds functional disability and characteristic neuroimaging (frontal and/or anterior temporal atrophy, hypometabolism or hypoperfusion). Finally, bvFTD 'with definite FTLD' requires histopathological confirmation or a pathogenic mutation. These revised criteria have a much higher sensitivity in comparison to the earlier criteria (Neary et al., 1998). Although the regional specificity of bvFTD's imaging markers is still under debate (Schroeter, 2012), incorporating these markers will greatly improve early *ante mortem* identification of bvFTD, which is particularly relevant for timely treatment – a paradigm shift suggested also for other dementia syndromes (Dubois et al., 2007; Gorno-Tempini et al., 2011).

In the last two decades, neuroimaging studies have revolutionized the understanding of cognitive functions in healthy subjects and in brain diseases (Derrfuss & Mar, 2009; Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011). Uniform coordinate systems enable comprehensive systematic and quantitative meta-analyses that might identify the prototypical neural networks involved in specific neuropsychiatric diseases, such as mood disorders, schizophrenia and dementia syndromes. Recent meta-analyses across imaging studies have applied the likelihood estimate method, the most refined and best-validated approach to coordinate-based voxelwise meta-analyses (Fox, Laird, & Lancaster, 2005; Glahn et al., 2008; Laird et al., 2005; Sacher et al., 2012; Schroeter & Neumann, 2011; Schroeter, Raczka, Neumann, & von Cramon, 2007, 2008, 2009; Turkeltaub, Eden, Jones, & Zeffiro, 2002). Here, two subtypes exist. The anatomical likelihood estimate (AnLE) method uses coordinates of peaks for atrophy, hypometabolism, or hypoperfusion during rest in patients if compared with control subjects, and determines brain regions that exhibit a higher convergence of these peaks across single studies than would arise by chance. The final AnLE map extracts the prototypical neural correlates of a specific disease based on large cohorts that cannot be investigated in single center studies. The activation likelihood estimate (AcLE) method, using the same algorithms like the AnLE method, was developed earlier to conduct meta-analyses across functional imaging studies, where subjects are stimulated with psychological stimuli.

Here, we explore the general potential of combined multimodal imaging meta-analyses with AnLE and AcLE methods to conceptualize – i.e., understand and predict – neuropsychiatric diseases. We chose bvFTD as a model disease, a 'molecular nexopathy' (Warren, Rohrer, & Hardy, 2012; Zhou, Gennatas, Kramer, Miller, & Seeley, 2012) disconnecting the 'social brain' (Adolphs, 2010). The rationale of our approach, combing three meta-analytic steps, is illustrated in Fig. 1.

1.1. *Identifying bvFTD's neural correlates*

Firstly, we identified all relevant imaging studies of bvFTD from the literature containing 417 patients and 406 control subjects. We conducted an AnLE meta-analysis separately for morphometric studies with magnetic resonance imaging (MRI) and imaging studies applying ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) during rest. This meta-analysis identified the prototypical networks essential for bvFTD, and thereby validated diagnostic criteria as suggested recently by an international consortium (Rascovsky et al., 2011).

1.2. *Extracting bvFTD's behavioral correlates*

Secondly, we wanted to place bvFTD in a framework of cognitive neuropsychiatry by relating these neural changes to clinical and cognitive impairments (Halligan & David, 2001). Former studies discussed results of AnLE meta-analyses simply by reviewing the literature, which may be biased by subjective presumptions and the specificity problem – the fact that specific brain regions might be related to highly diverse brain functions (Schroeter, Raczka, Neumann, & von