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Medial prefrontal functional connectivity—Relation to memory self-appraisal accuracy in older adults with and without memory disorders

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ABSTRACT

It is tentatively estimated that 25% of people with early Alzheimer's disease (AD) show impaired awareness of disease-related changes in their own cognition. Research examining both normative self-awareness and altered awareness resulting from brain disease or injury points to the central role of the medial prefrontal cortex (MPFC) in generating accurate self-appraisals. The current project builds on this work – examining changes in MPFC functional connectivity that correspond to impaired self-appraisal accuracy early in the AD time course. Our behavioral focus was self-appraisal accuracy for everyday memory function, and this was measured using the Memory Function Scale of the Memory Awareness Rating Scale – an instrument psychometrically validated for this purpose. Using regression analysis of data from people with healthy memory ($n = 12$) and people with impaired memory due to amnestic mild cognitive impairment or early AD ($n = 12$), we tested the hypothesis that altered MPFC functional connectivity – particularly with other cortical midline structures and dorsolateral prefrontal cortex – explains variation in memory self-appraisal accuracy. We spatially constrained (i.e., explicitly masked) our regression analyses to those regions that work in conjunction with the MPFC to evoke self-appraisals in a normative group. This empirically derived explicit mask was generated from the result of a psychophysiological interaction analysis of fMRI self-appraisal task data in a separate, large group of cognitively healthy individuals. Results of our primary analysis (i.e., the regression of memory self-appraisal accuracy on MPFC functional connectivity) were generally consistent with our hypothesis: people who were less accurate in making memory self-appraisals showed attenuated functional connectivity between the MPFC seed region and proximal areas within the MPFC (including subgenual anterior cingulate cortex), bilateral dorsolateral prefrontal cortex, bilateral caudate, and left posterior hippocampus. Contrary to our expectations, MPFC functional connectivity with the posterior cingulate was not significantly related to accuracy of memory self-appraisals. Results reported here corroborate findings of variable memory self-appraisal accuracy during the earliest emergence of AD symptoms and reveal alterations in MPFC functional connectivity that correspond to impaired memory self-appraisal.

1. Introduction

Individuals with Alzheimer's disease (AD) experience cognitive loss and emotional and behavioral changes over the time course of the disease. Currently, it is tentatively estimated that at least 25% of people with early AD show impaired awareness of disease-related changes that are occurring in themselves (Derouesne et al., 1999; Feher, 1991; Kaszniak & Zak, 1996; Mograbi, Brown, & Morris, 2009; Salmon et al., 2008; Starkstein, Jorge, Mizrahi, Adrian, & Robinson, 2007). Because self-appraisals guide much human behavior, incorrect self-appraisals regarding one's present-day abilities shown by many AD patients (alternately referred to as anosognosia or impaired self-awareness in this manuscript) can yield significant deleterious consequences – including important safety risks for patients and those around them (Cotrell & Wild, 1999; Starkstein et al., 2007) and distress in families and caregivers (Clare, Whitaker, et al., 2011; Rymer et al., 2002; Seltzer, Vasterling, Yoder, & Thompson, 1997). Furthermore, impaired awareness of one's own decline may delay medical consultation regarding incipient dementia and can interfere with treatment compliance (Arlt, Lindner,

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Rosler, & Von Renteln-Kruse, 2008; Griffith, Dymek, Atchison, Harrell, & Marson, 2005; Karlawish, Casarett, James, Xie, & Kim, 2005; Koltai, Welsh-Bohmer, & Schmechel, 2001). Thus, carefully characterizing the behavioral presentation of this symptom early in the AD time course and disseminating this information to health care providers is one important inroad to decreasing the prevalence of missed and delayed AD diagnosis and improving patient care (Bradford, Kunik, Schulz, Williams, & Singh, 2009). Investigating changes in brain activity that covary with the intactness of self-appraisal ability will improve our ability to identify and understand the causes of anosognosia and may point to methods for its treatment.

In the search for brain changes that contribute to anosognosia such as those shown in AD, several lines of research point to altered function of the medial prefrontal cortex (MPFC). Alexander Luria – a seminal voice in the study of how human brain function effects and is affected by a sense of self and one's social context – highlighted the (MPFC) as a key part of a functional neural system underlying accurate self-appraisal (Luria, 1972, 1973). Contemporary lesion and functional neuroimaging studies that measure self-appraisal by asking people to make ratings regarding personal characteristics, preferences, and values corroborate this notion (Amodio & Frith, 2006; Johnson et al., 2002, 2006; Johnson & Ries, 2010; Pronin, 2008; Schmitz & Johnson, 2007). Normative fMRI studies of this sort of self-appraisal yield reliable and robust activity in medial prefrontal and posterior cingulate regions (for reviews please see Johnson & Ries, 2010; Schmitz & Johnson, 2007). Observation of behavior changes in people with altered medial prefrontal structure and function secondary to brain injury (Prigatano, 2010; Schroeter, Ettrich, Menz, & Zysset, 2010), frontotemporal dementia (Bastin et al., 2011; Grossman et al., 2010; Neary et al., 1998; Orfei et al., 2010; Rankin, Baldwin, Pace-Savitsky, Kramer, & Miller, 2005; Schroeter, Raczka, Neumann, & von Cramon, 2008), and a variety of other neurodegenerative conditions (Rosen et al., 2010) underscores the MPFC's central role in generating accurate self-appraisals as well as for guiding social decision-making and theory of mind or empathy for others. Furthermore, in people with amnestic mild cognitive impairment (MCI), medial prefrontal and posterior cingulate blood-oxygen-level-dependent (BOLD) response to self-appraisal corresponds directly to the accuracy of cognitive self-appraisal (Ries et al., 2007).

With this foundation of evidence regarding MPFC involvement in self-appraisal, research has turned to the MPFC's involvement in networks of brain activity. The MPFC is a heteromodal region that possesses anatomic connections with a large number of other heteromodal and limbic regions (Price, 1999; Price & Drevets, 2010; Saleem, Kondo, & Price, 2008) responsible for drive and reward (e.g., anterior cingulate, nucleus accumbens, ventral tegmental area), mood (e.g., amygdala), and episodic, semantic, and autobiographical memory (e.g., posterior cingulate, lateral parietal lobe, hippocampus). Given that it is anatomically well-situated to integrate inputs important for self-appraisal, Schmitz and Johnson (2006) examined MPFC condition-dependent connectivity in the context of an fMRI self-appraisal task. This study found that BOLD response in dorsolateral prefrontal cortex (DLPFC) and bilateral hippocampal regions showed condition-dependent co-activation with dorsal MPFC that was modulated by self-appraisal. The amygdala, nucleus accumbens, and insula also showed increased condition-dependent connectivity with ventral MPFC during a self-appraisal task relative to a semantic task.

The goal of the current project was to investigate changes in MPFC functional connectivity that correspond to impaired self-appraisal accuracy – specifically appraisal of current memory ability. Participants providing data for this project included older adults, some of whom had documented memory impairment and a diagnosis of MCI or early AD and some of whom had healthy memories. In this manuscript we conceptualize MCI and early AD as lying on a continuum of disease progression (Dubois et al., 2007) and report their descriptive data (Table 1) as one group. Research suggests that awareness is domain specific (i.e., a person may be aware of deficits in one cognitive or affect domain and not another; Clare, Whitaker, et al., 2011), and in the present study of anosognosia early in the AD course, we chose to focus on awareness of memory decline because it is the earliest and most consistent symptom at this stage of the disease. Memory self-appraisal was operationally defined as each participant's explicitly expressed evaluation of his/her current memory ability (i.e., the participant's rating of how well he was presently generally able to perform memory tasks in daily life). To measure accuracy of these self-appraisals, we used the Memory Function Scale of the Memory Awareness Rating Scale (MARS) – an index psychometrically validated for this purpose in people with AD (Clare, Whitaker, & Nelis, 2010; Clare, Wilson, Carter, Roth, & Hodgesm, 2002). This scale involves administering two questionnaires asking about the participant's ability to perform memory tasks during everyday activities – a self-appraisal questionnaire is given to the participant and a parallel questionnaire is given to a person who knows the participant well. Memory appraisal accuracy is indexed via a discrepancy score between the two parallel forms of questionnaires – with the study partner's report considered to be the "truth" or gold standard. Because study partner reports can be influenced by perceived caregiver burden (Quinn, Clare, & Woods, 2009), we assessed this with the Zarit Burden Interview (Zarit, Reever, & Bach-Peterson, 1980), and we also verified study partner reports against a neuropsychological memory test (Hopkins Verbal Learning Test-Revised; HVLT-R). We expected our healthy control participants to show close correspondence with their study partners in their memory appraisals – thus showing intact memory self-appraisal ability. Based on prior findings, we expected individuals with memory impairment due to MCI and early AD to show a range of accuracy in their memory self-appraisals (Ries et al., 2007; Vogel et al., 2004). Using regression analysis, we tested the hypothesis that altered MPFC functional connectivity – particularly with other cortical midline structures – explains a significant portion of this variation in memory self-appraisal accuracy as measured by the Memory Function Scale. Furthermore, we expected that such a relationship exists independent of the severity of memory impairment. Therefore we included an index of learning (i.e., total number of items learned across trials on the HVLT-R), as a covariate in the regression analysis. In order to constrain our regression analyses to those regions that work in conjunction with the MPFC to evoke self-appraisals, we derived an explicit mask – generated from fMRI self-appraisal task data in a separate, large group of cognitively healthy individuals. In the analysis yielding this explicit mask, psychophysiologic interaction analysis was used to identify regions showing condition-dependent connectivity with the MPFC that was modulated by a self-appraisal context.

2. Materials and methods

2.1. Overall study design

The primary analysis examined how MPFC connectivity changes as a function of the accuracy of one's memory self-appraisals as measured by the memory function discrepancy (MFD) score (described in Section 2.3.2). Participants, behavioral methods, and neuroimaging methods that yielded data for these analyses are detailed in Sections 2.2, 2.3 and 2.4.2 respectively.

To reduce the risk of false positive (Type 1) statistical errors in these analyses, we chose to restrict (or explicitly mask) the above-described regression analysis to behaviorally relevant brain regions. To do this, we employed fMRI self-appraisal task data from a separate, large group ($N = 90$) of cognitively healthy adults (mean age: 58.7 ± 2.9), and we examined those brain regions that showed condition-dependent connectivity with the MPFC that was modulated by a self-appraisal context. Section 2.4.1 details the fMRI task design and psychophysiological interaction analysis methods used to derive this mask.