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Functional neuroanatomy of spatial sound processing in Alzheimer's disease

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ABSTRACT

Deficits of auditory scene analysis accompany Alzheimer's disease (AD). However, the functional neuroanatomy of spatial sound processing has not been defined in AD. We addressed this using a "sparse" fMRI virtual auditory spatial paradigm in 14 patients with typical AD in relation to 16 healthy age-matched individuals. Sound stimulus sequences discretely varied perceived spatial location and pitch of the sound source in a factorial design. AD was associated with loss of differentiated cortical profiles of auditory location and pitch processing at the prescribed threshold, and significant group differences were identified for processing auditory spatial variation in posterior cingulate cortex (controls > AD) and the interaction of pitch and spatial variation in posterior insula (AD > controls). These findings build on emerging evidence for altered brain mechanisms of auditory scene analysis and suggest complex dysfunction of network hubs governing the interface of internal milieu and external environment in AD. Auditory spatial processing may be a sensitive probe of this interface and contribute to characterization of brain network failure in AD and other neurodegenerative syndromes.

1. Introduction

"Auditory scene analysis", the process by which we make sense of our auditory environment (Bregman, 1990), entails demanding neural computations that are performed automatically and efficiently by the normal brain. Auditory scene analysis entails the disambiguation and tracking of sound sources in space and over time, and has been shown to engage brain mechanisms in auditory association cortex in the posterior superior temporal lobe and its connections (Alain et al., 2001, 2008; Altmann et al., 2008; Brunetti et al., 2005, 2008; Bushara et al., 1999; Warren and Griffiths, 2003; Weeks et al., 1999; Zimmer et al., 2006). This previous evidence supports a dual organization of dorsally and ventrally directed human cortical processing streams respectively mediating sound localization and identification, and broadly analogous to the "'what-where" dichotomy held to underpin visual object processing. The dorsal auditory stream via its inferior parietal and premotor projections is involved in preparing behavioral responses to sounds (Alain et al., 2001, 2008; Bushara et al., 1999; Warren et al., 2005; Weeks et al., 1999; Zimmer et al., 2006). However, auditory scene analysis is likely to involve additional cortical regions: in particular, the posterior medial cortical region (comprising posterior cingulate, precuneus and retrosplenial cortex: Leech and Sharp, 2014) has been implicated in orienting responses to auditory spatial stimuli (Bushara et al., 1999; Mayer et al., 2006, 2007; Zündorf et al., 2013), whereas insula may be engaged in processing aspects of auditory motion or integrating spatial with other sound characteristics (Altmann et al., 2008; Griffiths et al., 1994; Lewis et al., 2000). Furthermore, the analysis of natural auditory scenes generally entails simultaneous processing of spatial location and identity properties of sound sources in the environment (Bregman, 1990).

Recent studies have highlighted the relationship between peripheral hearing function, cognitive performance, and regional brain atrophy (Lin et al., 2011, 2014). However, in addition to any peripheral hearing effect, the distributed, complex neural computations of auditory scene analysis are likely to be particularly vulnerable to the cortical pathology of Alzheimer's disease (AD). Clinical experience suggests that patients with AD often have difficulty deciphering auditory information in busy acoustic environments (Golden et al., 2015b). AD has been shown to impair various

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processes underpinning the analysis of auditory scenes, including segregation and binding of sound streams (Golden et al., 2015a; Goll et al., 2012), perception of sound location and motion (Golden et al., 2015b; Kurylo et al., 1993), dichotic listening and auditory attention (Gates et al., 1996, 2008, 2011; Golob et al., 2001, 2009; Strouse et al., 1995). Furthermore, impaired auditory scene analysis may be a harbinger of AD, manifesting presymptomatically in carriers of pathogenic mutations causing familial AD (Gates et al., 2011; Golob et al., 2009). Deficits of auditory scene analysis in AD have been correlated with alterations of gray matter structure and function in posterior lateral and medial temporo-parietal cortices that overlap the substrates of auditory spatial and pitch pattern analysis identified in the healthy brain (Brunetti et al., 2005; Golden et al., 2015b; Goll et al., 2012; Patterson et al., 2002; Warren and Griffiths, 2003; Zündorf et al., 2013). These neuroanatomical correlates include core regions of the so-called "default-mode network": a brain network linking mesial temporal, lateral parietal, and prefrontal regions via a posterior medial cortical hub zone (Fransson and Marrelec, 2008; Raichle et al., 2001; Shulman et al., 1997) that has been identified previously as the principal target of the pathological process in AD (Buckner et al., 2005, 2008; Lehmann et al., 2010; Matsuda, 2001; Minoshima et al., 1997; Scahill et al., 2002; Seeley et al., 2009; Warren et al., 2012).

In earlier work, deactivation of the default-mode network on task engagement was interpreted as evidence that this network mediates stimulus-independent thought in the resting brain (Raichle et al., 2001; Shulman et al., 1997). However, the network also participates in active processes such as imagery (Buckner and Carroll, 2007; Buckner et al., 2008; Spreng and Grady, 2010; Zvyagintsev et al., 2013) which may relate to the online representation of auditory information. The precise role of the default-mode network in these processes and more particularly the functional impact of AD on this network (and indeed, on connected brain regions beyond the putative core network) have not been defined. Previous studies using task-related fMRI in AD have focused on memory (Pihlajamäki and Sperling, 2009; Sperling et al., 2010, 2003): although these studies have shown AD is associated with failure to deactivate the default-mode network normally during information encoding, it remains unclear whether this is a generic mechanism of AD-mediated dysfunction that extends to other kinds of information processing in sensory systems. Auditory scene analysis offers a clinically and anatomically relevant paradigm with which to probe AD-associated network dysfunction, whereas fMRI provides a means to assess the functional neuroanatomy of component cognitive processes and to correlate these with behavior and with structural network disintegration in AD. Previous functional neuroimaging studies assessing auditory processing in AD have been chiefly confined to the domain of memory (e.g., Dhanjal and Wise, 2014; Grossman et al., 2003a, 2003b; Peters et al., 2009; Rémy et al., 2005): these studies have revealed a complex profile of AD-associated network activity shifts. In previous work, we have shown that activation of inferior parietal cortex is increased during auditory scene analysis (the "cocktail party effect") in patients with AD relative to healthy individuals (Golden et al., 2015a). However, previous functional neuroimaging studies have not assessed the processing of sounds in space: decoding of spatial cues is fundamental to the analysis of natural auditory scenes, computationally demanding and deficient in AD (Golden et al., 2015b).

In this study, we used fMRI to assess the processing of sound sources located in space in patients with AD compared with healthy older individuals. We exploited a virtual acoustic space technique that simulates pinna filtering characteristics (Wightman and Kistler, 1989a, 1989b) to manipulate sound source location and pitch in a common paradigm in the scanner environment. Spatial location and pitch are both key auditory scene components, used in separating and tracking sound sources and information streams against the acoustic background (Bregman, 1990): although evidence for auditory spatial deficits in AD continues to be amassed (Golden et al., 2015b; Kurylo et al., 1993), the processing of pitch in AD may be modulated by context and in particular, whether pitch is varied within an auditory scene (Goll et al., 2011, 2012; Strouse et al., 1995). Although the existence of separable cortical substrates for processing pitch and spatial information has been established in the healthy brain (Warren and Griffiths, 2003), the extent of any such dichotomy in the dysfunctional cortex of AD remains unclear. Moreover, natural auditory scenes typically entail the joint processing of pitch and spatial information and these may interact (Chen et al., 2007). Accordingly, here we adopted a design in which location and pitch were varied factorially in sound sequences. In addition, we did not use an output task during scanning, as our primary interest here was to capture AD-associated alterations in obligatory, "bottom-up" brain mechanisms of spatial sound analysis, rather than task effects that might potentially be confounded by "top-down" attentional, mnestic, or effort factors; cognitive performance for processing relevant spatial sound parameters was instead assessed in post-scan behavioral testing. Based on prior cognitive and neuroanatomical evidence (Golden et al., 2015b; Goll et al., 2012), we hypothesized that AD would be associated with obligatorily altered cortical signatures of spatial sound analysis relative to healthy individuals, with loss of normal functional differentiation for the processing of pitch and spatial sound attributes. More specifically, we hypothesized a functional neuroanatomical correlate of this AD effect in posterior auditory association and temporo-parietal regions previously implicated in auditory spatial analysis and converging on the default-mode network (Golden et al., 2015b; Goll et al., 2012; Lewis et al., 2000; Warren and Griffiths, 2003; Zündorf et al., 2013).

2. Methods

2.1. Participants

Fourteen consecutive patients [6 women; mean (SD) age = 69.8 (6.3)] fulfilling criteria for typical amnestic AD (Dubois et al., 2007) and 16 healthy older individuals [9 women; mean (SD) age = 70.1 (5.0)] with no past history of neurological or psychiatric illness participated. No participant had a history of clinically significant hearing loss. At the time of participation, 12 AD patients were receiving symptomatic treatment with an acetylcholinesterase inhibitor and the remaining 2 were receiving memantine. The clinical diagnosis in the patient group was corroborated by a comprehensive neuropsychological assessment and volumetric brain MRI; no patient had radiological evidence of significant cerebrovascular damage. Demographic, clinical, and neuropsychological details for all participants are summarized in Table 1. The diagnosis of AD was further supported by cerebrospinal fluid examination (ratio total tau: beta amyloid1-42 >1 in 8 of 9 cases where cerebrospinal fluid data were available).

The study was approved by the local institutional ethics committee, and all participants gave written informed consent in accordance with the guidelines laid down in the Declaration of Helsinki.

2.2. Assessment of peripheral hearing

Peripheral hearing was assessed in all participants using a procedure adapted from a commercial screening audiometry software package (AUDIO-CDTM, http://www.digital-recordings.com/audiocd/audio.html). This peripheral audiometry test was administered via headphones from a notebook computer in a quiet room; participants were presented with continuous tones at 1 of 5 frequencies (500, 1000, 2000, 3000, 4000 Hz) that were initially