

Impairments of auditory scene analysis in Alzheimer's disease

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Parsing of sound sources in the auditory environment or 'auditory scene analysis' is a computationally demanding cognitive operation that is likely to be vulnerable to the neurodegenerative process in Alzheimer's disease. However, little information is available concerning auditory scene analysis in Alzheimer's disease. Here we undertook a detailed neuropsychological and neuroanatomical characterization of auditory scene analysis in a cohort of 21 patients with clinically typical Alzheimer's disease versus age-matched healthy control subjects. We designed a novel auditory dual stream paradigm based on synthetic sound sequences to assess two key generic operations in auditory scene analysis (object segregation and grouping) in relation to simpler auditory perceptual, task and general neuropsychological factors. In order to assess neuroanatomical associations of performance on auditory scene analysis tasks, structural brain magnetic resonance imaging data from the patient cohort were analysed using voxel-based morphometry. Compared with healthy controls, patients with Alzheimer's disease had impairments of auditory scene analysis, and segregation and grouping operations were comparably affected. Auditory scene analysis impairments in Alzheimer's disease were not wholly attributable to simple auditory perceptual or task factors; however, the between-group difference relative to healthy controls was attenuated after accounting for non-verbal (visuospatial) working memory capacity. These findings demonstrate that clinically typical Alzheimer's disease is associated with a generic deficit of auditory scene analysis. Neuroanatomical associations of auditory scene analysis performance were identified in posterior cortical areas including the posterior superior temporal lobes and posterior cingulate. This work suggests a basis for understanding a class of clinical symptoms in Alzheimer's disease and for delineating cognitive mechanisms that mediate auditory scene analysis both in health and in neurodegenerative disease.

Keywords: Alzheimer's disease; auditory scene analysis; auditory processing; voxel-based morphometry

Abbreviations: ASA = auditory scene analysis

Introduction

In our daily lives we are surrounded by multiple sounds generated by a range of sources in the environment. To make sense of these sound mixtures, the auditory brain must determine which acoustic properties belong to which sound sources. In cognitive terms, this process consists of parsing the auditory scene into constituent 'auditory objects'. The cognitive and neuro-anatomical bases for object formation in the auditory domain have been explored previously (e.g. O'Leary and Rhodes, 1984; Bregman, 1990; Woods and Colburn, 1992; Kubovy and Van Valkenburg, 2001; Binder *et al.*, 2004; Griffiths and Warren, 2004; Husain *et al.*, 2004; Zatorre *et al.*, 2004; Goll *et al.*, 2010). Here, we define 'auditory object' operationally as a collection of acoustic properties that is bound together and disambiguated from background noise (after Goll *et al.*, 2010). The processing of auditory scenes is a formidable and multicomponent computational problem, requiring deconvolution of a complex, dynamic sound mixture and accurate perceptual representation of auditory objects embedded in the scene (Griffiths and Warren, 2002; Goll *et al.*, 2010). One everyday example of such processing in action is the familiar 'cocktail party effect', the ability to rapidly and automatically detect one's own name spoken across a noisy room. The cognitive operations whereby object properties are segregated from the acoustic background (object segregation) and bound together as discrete perceptual entities (object representation) are collectively termed 'auditory scene analysis' (ASA; Bregman, 1990).

In general, ASA is mediated by both 'bottom-up' and 'top-down' mechanisms (Bregman, 1990; Alain and Arnott, 2000; Snyder and Alain, 2007; Winkler *et al.*, 2009). Bottom-up mechanisms involve the organization of object features according to acoustic properties (Bregman, 1990; Fishman and Steinschneider, 2010); sound properties that are harmonically related or coincident in space or time are likely to emerge from the same object whereas sound properties that arise from different spatial locations or are widely spaced in frequency or time tend to come from different objects. Top-down mechanisms involve the organization of acoustic components into perceptual object representations based on prior experience (for example by matching incoming acoustic data with stored perceptual object representations, or 'auditory templates': Griffiths and Warren, 2002) or executive processes (especially working memory and attention). Such mechanisms tend to bias parsing towards the formation of particular object representations, and facilitate the tracking of auditory sequences (or 'streams') over time. The interaction of mechanisms during ASA is illustrated in the dual-stream 'Horse-Morse' paradigm (van Noorden, 1975), in which two sequences of tones (one at a lower pitch and faster rate than the other) are superimposed to create a percept of sounds organized as either one combined stream or two separate streams: here, perceptual segregation into two streams can be promoted by bottom-up processing (e.g. tones further apart in frequency), or top-down processing (e.g. via stored perceptual representations of segregated objects or attentional shifts following changes in task instructions; Bregman, 1990; Moore and Gockel, 2002; Snyder and Alain, 2007).

A growing body of functional imaging work in healthy subjects has implicated a network of brain areas in ASA: these include primary and association auditory cortices (Deike *et al.*, 2004, 2010; Gutschalk *et al.*, 2007; Schönwiesner *et al.*, 2007; Wilson *et al.*, 2007; Overath *et al.*, 2010; Schadwinkel and Gutschalk, 2010; Smith *et al.*, 2010), and parietal and frontal regions (e.g. Cusack *et al.*, 2005; Schönwiesner *et al.*, 2007; Teki *et al.*, 2011). Such studies have begun to define distinct brain substrates and time windows for particular ASA subprocesses. For example, in a combined functional MRI-EEG study based on an auditory 'oddball' detection paradigm (Schönwiesner *et al.*, 2007), three distinct cortical regions were associated with temporally successive stages of ASA: primary auditory cortex with initial object segregation (a bottom-up process); posterior superior temporal gyrus and planum temporale with the detailed perceptual representation of segregated objects (a top-down process guided by prior knowledge of auditory objects); and mid-ventrolateral prefrontal cortex with attentional allocation (a top-down executive process). Additionally, a number of functional MRI studies have emphasized the role of planum temporale in the top-down process of matching incoming acoustic data with stored auditory templates during ASA (Deike *et al.*, 2004, 2010; Gutschalk *et al.*, 2007; Wilson *et al.*, 2007; Overath *et al.*, 2010; Smith *et al.*, 2010). Additional areas extrinsic to auditory cortex have also been implicated in the top-down perceptual segregation of auditory objects. One functional MRI study using a 'dual stream' task showed greater activity in the inferior parietal sulcus when two streams were perceived compared to one (Cusack *et al.*, 2005). The activity of posterior cingulate cortex and adjacent precuneus is modulated during tracking and mental representation of information in sound as well as other sensory domains, and this region is likely to have a key role in the evaluation of events in the auditory environment in relation to behavioural goals and inner states (Sieroka *et al.*, 2003; Laurens *et al.*, 2005; Lockwood *et al.*, 2008; Sadaghiani *et al.*, 2009; Daselaar *et al.*, 2010; Hunter *et al.*, 2010).

Little is known about ASA in human neurological disease. Cusack *et al.* (2000) found that patients with focal right parietal lesions showed selective deficits of auditory attention when comparing features distributed across multiple auditory objects, but not features within single auditory objects. These findings suggest that the non-dominant parietal lobe may have a critical role in the perceptual organization of more complex auditory scenes. The study of ASA mechanisms may be equally pertinent in neurodegenerative diseases that involve the posterior temporal and parietal lobes: the most important candidate is Alzheimer's disease, and indeed, patients with Alzheimer's disease commonly complain of difficulty in tracking auditory information streams (e.g. following conversations in the presence of background noise or over a noisy telephone line). Further, psychoacoustic deficits for ASA on verbal information streams (sentence competition tasks; Gates *et al.*, 1996, 2002, 2008, 2011), and altered cortical function during auditory 'oddball' detection and other tasks relevant to ASA (Golob *et al.*, 2007, 2009) have been documented early in the course of Alzheimer's disease or pre-symptomatically. This evidence supports the clinical impression that ASA impairments may be an early manifestation of Alzheimer's disease. As Alzheimer's disease evolves it characteristically blights a distributed brain

network encompassing key cortical areas for non-verbal sound processing in the temporal and parietal lobes, including brain substrates implicated in ASA (Buckner *et al.*, 2009; Seeley *et al.*, 2009; Zhou *et al.*, 2010). These damaged regions are likely to overlap with temporoparietal areas engaged in working memory (Stopford *et al.*, 2007, 2010), though the nature of working memory deficits in Alzheimer's disease (and in particular, the role of modality-specific working memory processes) is a complex issue that has not been fully resolved (Huntley and Howard, 2010). Available evidence provides a rationale for investigating ASA in Alzheimer's disease. However, the cognitive basis for any Alzheimer's disease-associated deficit of ASA has not been defined.

In this study, we conducted a systematic neuropsychological investigation of ASA in a cohort of patients with clinically diagnosed, typical Alzheimer's disease. We designed a novel battery to probe two generic processes of fundamental relevance to ASA: the segregation of coincident sounds into separate sound objects; and the perceptual grouping of temporally spaced sounds into a single extended object (a sound 'stream'). In designing the experimental battery we sought to minimize extraneous cognitive demands (for example, those associated with sound identification or labelling, or speech processing), and to assess the contribution of auditory perceptual, task and general neuropsychological factors that might contribute to overall performance during ASA. We hypothesized that patients with Alzheimer's disease would exhibit deficits of ASA even after taking into account other relevant cognitive factors. In order to assess the neuroanatomical associations of ASA performance in Alzheimer's disease, we analysed patients' structural brain MRI data using voxel-based morphometry. We hypothesized that performance on both ASA tasks would be correlated with grey matter volume in bi-hemispheric posterior cortical areas including the posterior superior temporal lobe, temporoparietal junction and posterior cingulate.

Materials and methods

Participants

Twenty-one consecutive patients [12 females; mean (SD) age = 65.0 (7.9) years] with a clinical diagnosis of typical Alzheimer's disease were recruited from a tertiary cognitive disorders clinic. Here we use the term 'typical Alzheimer's disease' to refer to a syndrome led by impairment of episodic memory with additional multi-domain cognitive deficits, in line with current neuropsychological usage (e.g. Stopford *et al.*, 2010). All patients had a structured clinical history and neurological examination by an experienced cognitive neurologist. A diagnosis of Alzheimer's disease was based on revised NINCDS-ADRDA criteria for probable Alzheimer's disease (McKhann *et al.*, 1984; Dubois *et al.*, 2007) with a corroborating history of episodic or topographical memory impairment as the leading symptom. Patients had brain MRI showing features typical of Alzheimer's disease (bilateral symmetrical hippocampal atrophy with less marked background cerebral atrophy) in all but two cases (one showing diffuse atrophy without hippocampal emphasis, and one with a normal scan); no scan showed significant cerebrovascular damage. The Alzheimer's disease group here contained relatively young patients [mean age (SD) 65.0 (7.9) years]. However, this disease group was age-matched to a healthy

control group comprising 18 subjects [12 females; mean age (SD) 65.7 (7.5) years] with no history of neurological or psychiatric illness.

Patients underwent a comprehensive general neuropsychological assessment in order to provide background data and to assist interpretation of the experimental auditory battery. A subset of these assessments, measuring general (non-auditory) cognitive abilities that might potentially influence performance on the experimental tests were also completed by controls. These latter assessments comprised digit span (indexing auditory working memory; Wechsler, 1987), visuospatial span (indexing non-verbal working memory; Wechsler, 1999), and a reaction time test. The reaction time test was adapted from Stuss *et al.* (2005), and measured the latency of button-press responses to visual stimuli that were presented intermittently and unpredictably on a notebook computer screen. A 'sustained attention' condition comprised 10 presentations of the letter 'X'; subjects were instructed to watch the screen and press a response button upon seeing 'X'. Additionally, a 'sustained-plus-selective attention' condition comprised 10 presentations of the letter 'X' and 10 presentations of the letter 'O' in a fixed random order; subjects were instructed to press the response button upon seeing the letter 'X', but not the letter 'O'. Mean reaction time in the 'sustained-plus-selective attention' condition for each subject was calculated for use in the main experimental analyses (further details in the online Supplementary material).

Subjects with clinically significant hearing loss were excluded from the study; however, given the prevalence of age-related hearing problems in older adult populations, subjects with mild hearing loss were retained, and the ensuing effects upon assessments of auditory cognition were measured (below). Demographic and general neuropsychological data for all subjects are summarized in Table 1. Patient and control groups were well matched for gender, age and years of education. All subjects gave written informed consent to participate and the study was conducted in accord with the guidelines laid down in the Declaration of Helsinki.

Peripheral hearing assessment

To assess any effects of hearing loss on performance in the experimental tasks, all subjects underwent pure tone audiometry, administered via headphones from a notebook computer in a quiet room. The procedure was adapted from a commercial screening audiometry software package (AUDIO-CD™, Digital Recordings, <http://www.digital-recordings.com/audiocd/audio.html>). Five frequency levels (0.5, 1, 2, 3 and 4 KHz) were assessed: at each frequency, subjects were presented with a continuous tone that slowly and linearly increased in intensity. Subjects were instructed to tap as soon as they could detect the tone; this response time was measured and stored for offline analysis. The mean value for three presentations of the same tone in the right ear (or the left ear in the case of one patient with Alzheimer's disease who reported unilateral right-sided hearing loss) was taken as the detection threshold for that frequency.

Assessment of auditory scene analysis

Two novel neuropsychological tests were developed to probe generic ASA processes in cognitively impaired subjects: 'ASA-segregation', requiring the segregation of coincident sound objects on the basis of timbral cues; and 'ASA-grouping', requiring the grouping of temporally spaced sound objects into a single stream on the basis of pitch cues. In designing these tests we wished to minimize any requirement for semantic processing of the constituent sounds. However, from a clinical perspective, the segregation task indexes a process involved in recognizing a salient sound (e.g. one's own name) within the auditory

Table 1 Demographic and neuropsychological group data

Measure	Alzheimer's disease	Control
Gender (male:female)	9:12	6:12
Age (years)	65.0 (7.9)	65.7 (7.5)
Education (years)	18.5 (3.0)	18.5 (3.8)
Clinical disease duration (years)	5.9 (2.5)	–
Mini-mental state examination, raw score (/30)	22.1 (4.2)	–
WASI (IQ)		
Verbal	101.1 (16.9)	–
Performance	87.3 (19.4) ^a	–
British picture vocabulary Scale ^b (IQ)	109.5 (17.4)	–
Recognition memory test, Z-score		
Words	–1.4 (0.6) ^a	–
Faces	–1.3 (0.7) ^a	–
Graded naming test, Z-score	–0.8 (1.5)	–
Arithmetic, Z-score	–1.1 (1.0)	–
Object decision, Z-score	–0.4 (1.2)	–
Stroop, Z-score		
Colour naming	–1.5 (1.4) ^a	–
Word reading	–1.2 (1.6)	–
Interference ^c	–1.5 (1.2) ^a	–
Digit span, raw score (/12)		
Forwards	7.5 (2.2)	9.8 (1.6)
Reverse	5.2 (2.8)	8.1 (3)
Visuospatial span, raw score (/12)		
Forwards	5.2 (2.5)	7.4 (2)
Reverse	3.9 (2.1)	7.2 (0.9)
Reaction time test, mean time (ms)		
Sustained	520.7 (264.9)	302.8 (79.0)
Sustained plus selective	647.8 (219.4)	461.8 (88.3)

Mean (SD); unless otherwise indicated.

a Mean group score <10th percentile of published normative data; values in bold: Alzheimer's disease group differs from experimental control group ($P < 0.05$, inferred from bootstrapped confidence intervals).

b No published normative data exist in older populations and thus normative data for 18 year-old subjects were used.

c Three subjects with Alzheimer's disease were too impaired to attempt the interference condition of the Stroop test.

Arithmetic = Graded difficulty Arithmetic test (Jackson and Warrington, 1986); Digit span = WMS-R (Wechsler Memory Scale – Revised) Digit Span (Wechsler, 1987); Graded naming test (McKenna and Warrington, 1983); Mini-Mental State Examination (Folstein *et al.*, 1975); Object Decision = test of visual object perception taken from the Visual Object and Space Perception Battery (VOSP, Warrington and James, 1991); Recognition memory test (Warrington, 1984); Stroop = D-KEFS Stroop test (Delis *et al.*, 2001); Visuospatial span = WMS-III Spatial Span (Wechsler, 1997); WASI = Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999).

environment, while the grouping task indexes a process involved in tracking a conversation (a particular speaker) in the presence of background noise. In order to equate overall stimulus complexity and cognitive demands other than the ASA process of interest, the two ASA tests were based on similar sound elements and response procedures. Each ASA test comprised three sub-tests: the ASA task proper, and two baseline control tests assessing subsidiary cognitive processes which in themselves do not constitute ASA, but which were predicted to affect performance in the ASA tasks. These control tests comprised a 'perceptual-cue' control test, to assess whether subjects could discriminate changes in perceptual cues (timbre or pitch) driving the relevant ASA test; and a 'task-response' test, to assess whether subjects

could reliably comply with the task response requirements of the relevant ASA test.

Auditory scene analysis segregation assessment

Main test

Stimuli (20 trials) were created digitally in Matlab 7.2[®] (The MathWorks, Inc.) by superimposing two sequences of harmonic sounds to create composite continuous sounds each with overall duration 10 s. A schematic of the test is presented in Fig. 1; examples of stimuli are provided in the Supplementary material. On every trial, one sound sequence had a timbre designated as the 'target' timbre, T_t , while the other had a distinct 'distractor' timbre, T_d . Four different distractor timbres, each distinct from T_t , were randomly distributed across the stimulus set to guard against any idiosyncratic effects that might follow the superposition of a particular timbre pair. Each sound element had the same temporal envelope (amplitude modulated at 80 Hz), pitch (283 Hz) and bandwidth (2950 Hz); timbre was manipulated by changing spectral shape within this frequency range. On every trial, the T_d sequence comprised 1 s intervals of sound separated by 1 s inter-sound gaps. Two experimental conditions were created by varying the temporal pattern of the T_t sequence, which was either continuous (10 trials) or intermittent with 1 s intervals of sound separated by 1 s inter-sound gaps mirroring the temporal pattern of the T_d sequence (10 trials). In the 'intermittent' condition, the intensity level of T_d was increased to match the overall intensity level in the 'continuous' condition. The task on each trial was to decide whether T_t sounds were 'long' (i.e. continuous) or 'on-off' (i.e. intermittent).

Perceptual-cue control

This control test was intended to establish that subjects were reliably able to detect timbre changes. Ten sound sequences were presented, five with continuous fixed timbre T_t , and five with timbre alternating between T_t and T_d . The four distinct T_d timbres described above were randomly distributed across the latter five stimuli; across the set of sequences, the temporal patterns used matched those of the sequences in the main test (Fig. 1; stimulus examples in the Supplementary material). The task on each trial was to decide if the sound was 'same' or 'changing'.

Task-requirement control

This control test was intended to establish that subjects could comply with the requirement to report continuous and intermittent temporal patterns. Ten sequences of sounds with timbre T_t were presented, five continuous and five intermittent; the temporal pattern of sequences matched those used in the main test (Fig. 1; stimulus examples in the Supplementary material). The task on each trial was to decide whether the sound was 'long' (i.e. continuous) or 'on-off' (i.e. intermittent).

Auditory scene analysis grouping assessment

Main test

Stimuli (20 trials) were created digitally in Matlab (MathWorks[™]) by superimposing two sequences of harmonic sounds to create composite sound sequences, each with overall duration 12 s; each individual sound element in a sequence had duration 60 ms with a flat temporal and spectral envelope and fixed frequency bandwidth (2950 Hz). A schematic of the stimuli is presented in Fig. 2; examples of stimuli are provided in the Supplementary material. For every stimulus, one of the component sequences was isochronous (fixed inter-sound interval 135 ms) and the other sequence was anisochronous (inter-sound interval varying pseudorandomly between 210 and 930 ms). Individual sounds were assigned one of two pitches, either a target pitch

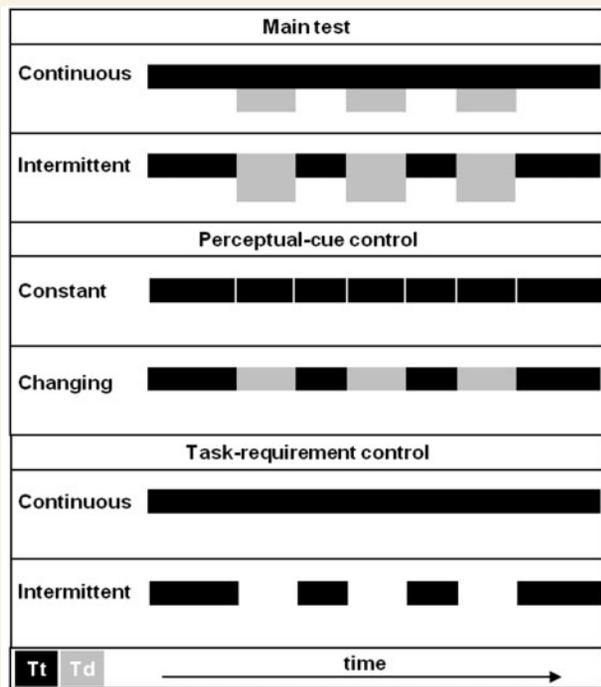


Figure 1 ASA-segregation assessment. Conditions in the three subtests of the ASA-segregation assessment (the ASA test and the perceptual-cue and task-requirement control tests) are shown schematically. Oblongs represent individual sound elements; for each element, width indicates relative duration and depth indicates relative intensity. Td = distractor timbre; Tt = target timbre.

($Pt = 423$ Hz) or a distractor pitch ($Pd = 237$ Hz); these pitch values were chosen such that they did not align with any familiar tonal interval from western musical scales. To create two experimental conditions, the distribution of Pt and Pd across the sound elements of the two superimposed sequences was varied from trial to trial. In the 'even' condition (10 trials), all sounds in the isochronous sequence had pitch Pt , while all sounds in the anisochronous sequence had pitch Pd . In the 'uneven' condition (10 trials), Pt was distributed between the isochronous and anisochronous sequences such that the temporal sequence of Pt sounds was itself anisochronous. This design ensured that the overall temporal distribution of sound elements (irrespective of pitch) and the mean rate of presentation of sounds with the target pitch were matched between conditions. The task on each trial was to decide whether Pt sounds were 'even' or 'uneven'.

Perceptual-cue control

This control test was intended to establish that subjects were reliably able to detect pitch differences. Ten isochronous sequences were presented, five with pitch fixed at Pt and five with pitch changing between Pt and Pd ; the tempi of the sequences matched those used in the main test (Fig. 2; stimulus examples in the Supplementary material). The task on each trial was to decide if the pitch was 'same' or 'changing'.

Task-requirement control

This control test was intended to establish that subjects could comply with the requirement to report even and uneven temporal patterns.

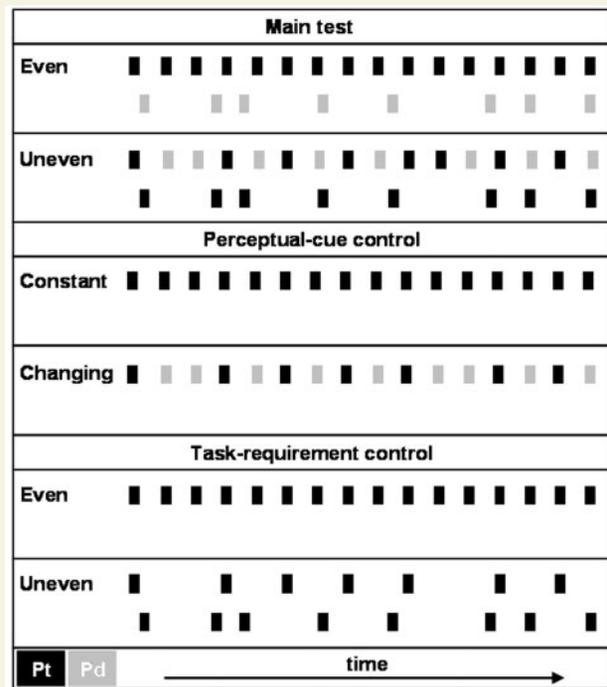


Figure 2 ASA-grouping assessment. Conditions in the three subtests of the ASA-grouping assessment (the ASA test and perceptual-cue and task-requirement control tests) are shown schematically. Oblongs represent individual sound elements; for each element, width indicates relative duration. The vertical position of sound elements within each condition here is arbitrary and intended only to display the isochronous and anisochronous sequences. Pd = distractor pitch; Pt = target pitch.

Ten sequences of sounds with pitch Pt were presented, five isochronous and five anisochronous; the temporal pattern of sequences matched those used in the main test (Fig. 2; stimulus examples in the Supplementary material). The task on each trial was to decide whether the sequence was 'even' or 'uneven'.

Auditory scene analysis test procedure

All sounds were presented as digital wavefiles from a notebook computer binaurally via Sennheiser HD 280-Pro headphones at a comfortable sound pressure level of at least 70 dB. Each ASA assessment was administered in a fixed order: perceptual-cue control, task-requirement control, main test. Within each subtest, trials were presented in a fixed randomized order. Response options were displayed in both verbal and diagrammatic form, as simplified versions of the schematics shown in Figs 1 and 2 and Supplementary Fig. 1. Responses could be made either verbally or by pointing, and were recorded for off-line analysis. Subjects were familiarized with task requirements prior to each test (using example stimuli not administered during the subsequent assessment). No feedback about performance was given during the assessment and no time limit was imposed on subject responses.

Behavioural analysis

General neuropsychological functions

For the majority of tests in the general neuropsychological assessment (Table 1), raw results were transformed into standardized (IQ or Z) scores based on published norms for subsequent analysis. For the

Mini-Mental State Examination and for tests also completed by the experimental control group, scores were analysed in raw format. For each test, linear regression was used to investigate the association of group with performance, adjusted for age and gender where score standardization had not already accounted for these factors.

Peripheral hearing

To examine the association of group with hearing, separate linear regression analyses were conducted for each of the frequency levels tested, adjusted for age and gender.

Auditory scene analysis assessments

Linear regression models were used to investigate the association of scores for each ASA test with group (control, Alzheimer's disease). Separate models were evaluated for each auditory test, adjusted for age, gender and performance on the relevant perceptual-cue control test (Model 1). Three further models also included a general neuropsychological measure that was anticipated to contribute to ASA performance as an additional covariate: raw total score in reverse digit span, indexing auditory working memory (Model 2), raw total score in reverse visuospatial span, indexing non-verbal working memory (Model 3), and mean reaction time derived from the 'sustained-plus-selective attention' condition of the reaction time test, indexing a combination of sustained and selective attention (Model 4).

An ASA discrepancy score (defined as score in the main ASA-grouping test minus score in the main ASA-segregation test) was calculated for each subject, in order to examine individual performance patterns. Finally, a correlation analysis (Pearson's rho) within the Alzheimer's disease group only was used to assess the relation between scores on the two main ASA tests.

General statistical methods

Owing to the relatively small group numbers in the study and large numbers of subjects performing at the test maxima, in general data did not meet normality assumptions. Therefore statistical inferences were made using bootstrapped confidence intervals (95%, bias-corrected, accelerated with 2000 replications).

Neuroimaging data

Brain image acquisition

T₁-weighted volumetric magnetic resonance images were acquired on a Siemens Trio TIM 3T scanner (Siemens Medical Systems) for 20 patients with Alzheimer's disease. Images were acquired using a 3D magnetization prepared rapid gradient echo (MP-RAGE) sequence producing 208 contiguous 1.1 mm thick sagittal slices with 28-cm field of view and a 256 × 256 acquisition matrix, giving approximately isotropic 1.1 mm cubic voxels; a 32-channel head coil was used (apart from two subjects for whom a 12-channel coil was used). Scans were bias-corrected using a non-parametric, non-uniform intensity normalization algorithm ('N3'; Sled *et al.*, 1998), with modifications for use with 3T scans (Boyes *et al.*, 2007).

Neuroimaging analysis

For the voxel-based morphometry analysis, magnetic resonance brain images were preprocessed using Matlab[®] and SPM8 software (Statistical Parametric Mapping, Version 8; <http://www.fil.ion.ucl.ac.uk/spm>) with default settings for all parameters; normalization was performed using the DARTEL toolbox (Ashburner, 2007; further details in the Supplementary material). Associations between regional grey matter volume and performance in each ASA test separately were assessed in the Alzheimer's disease group using voxel-wise linear regression models (one subject with Alzheimer's disease failed to complete the ASA-segregation test, and was therefore not included in the

corresponding statistical model). Scanner coil (32 or 12 channel), total intracranial volume, and age were included as covariates. Total intracranial volume was measured outside SPM using a previously described procedure (Whitwell *et al.*, 2001). An explicit analysis mask was used to exclude any voxels for which >20% of the images had an intensity value of <0.1; this procedure has been shown to reduce anatomical bias in subjects with substantial regional atrophy (Ridgway *et al.*, 2009).

Associations between grey matter volume and behavioural performance were assessed over the whole brain and within three regions of interest specified by our prior anatomical hypotheses. Small volumes covering the posterior superior temporal lobe and temporal parietal junction in each hemisphere, and a region including the posterior cingulate and precuneus were created manually in MRIcron[®] (<http://www.cabiatl.com/mricro/mricron/index.html>) from a study-specific template image (further details in the Supplementary material). A voxel-wise statistical threshold of $P < 0.05$, family-wise error corrected for multiple comparisons was applied in all analyses. Statistical parametric maps were displayed as overlays on the study-specific template.

Results

General neuropsychological functions

The Alzheimer's disease group was mildly to moderately impaired (performance above the fifth percentile but below the 10th percentile) on measures of performance IQ, verbal and visual recognition memory, and executive function (Table 1). On all tests performed both by the Alzheimer's disease group and the present healthy control group (digit span, visuospatial span, reaction time), patients performed significantly worse than controls (all $P < 0.05$).

Peripheral hearing

Sound detection thresholds for four of the five frequency levels examined (0.5, 2, 3 and 4 kHz) did not differ between the Alzheimer's disease and control groups (Supplementary Table 1). Detection threshold in the Alzheimer's disease group with respect to controls was raised at 1 kHz; however this rise was small (equivalent to a mean intensity increase of ~5 dB). Overall, these results suggest that peripheral hearing was similar between the Alzheimer's disease and healthy control groups.

Auditory scene analysis assessments

Raw data for the experimental auditory tests are displayed in Fig. 3. Auditory performance data for each test are summarized in Table 2. The association of ASA scores (for each test separately) with the factor of group and a subset of neuropsychological measures (digit span, visuospatial span and reaction time) are presented in Table 3. One patient with Alzheimer's disease failed to complete the ASA-segregation test due to time constraints; all other tests were completed by all subjects.

The Alzheimer's disease group showed deficits relative to the healthy control group on both the ASA-segregation and ASA-grouping tests (Table 3), though there was a wide spread of performance within the patient cohort (Fig. 3). The magnitude of the deficit and the range of performance within the Alzheimer's disease group was similar for both the ASA-segregation and ASA-grouping tests. For each ASA test, there was strong evidence

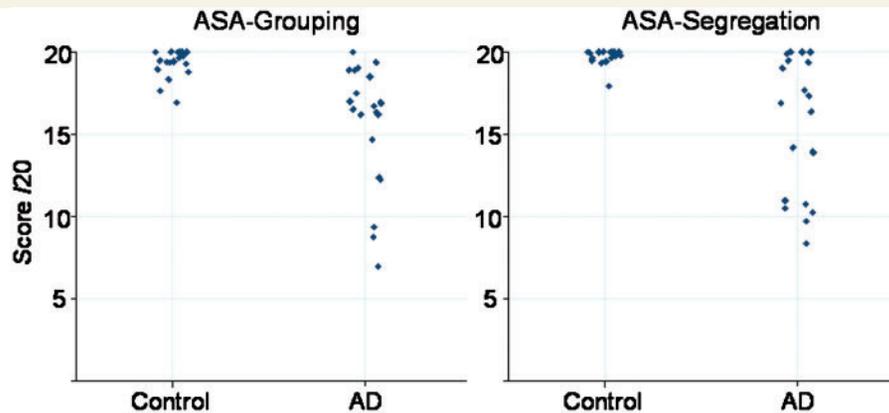


Figure 3 Raw ASA data: patients with Alzheimer's disease (AD) and healthy controls.

Table 2 ASA summary statistics: patients with Alzheimer's disease and healthy controls

Test	Task requirement control test (/10)		Perceptual cue control test (/10)		Main ASA test (/20)	
	Alzheimer's disease	Control	Alzheimer's disease	Control	Alzheimer's disease	Control
ASA-segregation ^a	10.0 (0.0), 10	10.0 (0.0), 10	9.4 (1.0), 7	10.0 (0.0), 10	15.5 (4.2), 9	19.9 (0.5), 18
ASA-grouping	10.0 (0.0), 10	10.0 (0.0), 10	9.9 (0.5), 8	10.0 (0.0), 10	15.7 (3.8), 7	19.4 (0.9), 17

Mean (SD), minimum.

a For the Alzheimer's disease group, the number of subjects was 20 (one patient failed to complete this test).

Table 3 Association of ASA scores with group and neuropsychological measures

Model	ASA test	Model covariates	Mean ^a (95% CI)	Covariate	Mean ^b (95% CI)
1	Seg	Group, age, gender, control test	−3.3 (−6.0 to −1.6)	Control test	2.0 (0.5 to 3.2)
	Group		−3.7 (−5.9 to −2.2)	control test	1.7 (−2.7 to 4)
2	Seg	Group, age, gender, control test, DS-R	−2.6 (−4.8 to −1.1)	DS-R	0.3 (0.0 to 0.7)
	Group		−2.8 (−4.8 to −1.1)	DS-R	0.4 (0.1 to 0.8)
3	Seg	Group, age, gender, control test, VS-R	−1.7 (−5.7 to 0.0)	VS-R	0.6 (−0.3 to 1.5)
	Group		−1.0 (−2.9 to 1.2)	VS-R	0.9 (0.2 to 1.6)
4	Seg	Group, age, gender, control test, RT-Sel.	−1.7 (−3.5 to −0.3)	RT-Sel.	0.0 (0.0 to 0.0)
	Group		−2.6 (−5.2 to −1.0)	RT-Sel.	0.0 (0.0 to 0.0)

a Difference in ASA test score (Alzheimer's disease-control).

b Change in ASA test score for one unit increase in covariate.

Effects with $P < 0.05$ (inferred from bootstrapped confidence intervals) are shown in bold. Effects of covariates are assumed constant across groups (no interaction terms fitted).

DS-R = Digit span reverse; Group = ASA-grouping test; RT-Sel = mean reaction time in the 'sustained-plus-selective attention' condition of the reaction time test; Seg = ASA-segregation test; VS-R = visuospatial span reverse.

for a difference in performance on ASA tests between controls and patients with Alzheimer's disease after adjusting for age, gender and control (perceptual-cue) test performance (Model 1). Further adjustment for auditory verbal working memory or sustained/selective attention did not substantially alter this result (Models 2 and 3; Table 3). However, adjustment for non-verbal (visuospatial) working memory performance (Model 3) explained some of the difference between controls and patients with Alzheimer's disease, with no evidence for a group difference on the ASA-grouping test after adjustment for this measure. Finally, performance on the

ASA-segregation and ASA-grouping tests was correlated [Pearson's $r = 0.68$; 95% confidence interval (CI): 0.40–0.86].

The pattern of ASA discrepancy scores among subjects differed between the Alzheimer's disease and control groups (Supplementary Fig. 2). Most control subjects showed either no ASA discrepancy or a small discrepancy, whereas patients with Alzheimer's disease showed a spread of ASA discrepancy scores; in support of these observations, there was good evidence that the modulus of the ASA discrepancy scores (i.e. ignoring the direction of the difference) differed by group (Mann-Whitney U test, $P < 0.01$).

However, there was no evidence for a group difference in ASA discrepancy taking into account the direction of scores (Mann–Whitney U test, $P = 0.8$). It is noteworthy that patients with Alzheimer's disease showed a similar frequency of discrepancies favouring either the ASA-segregation or the ASA-grouping test whereas control subjects showed discrepancies favouring only the ASA-grouping test, suggesting qualitatively different performance profiles at an individual level.

Neuroimaging findings

Neuroanatomical associations of ASA performance in the Alzheimer's disease cohort are shown in Fig. 4. No significant associations between behavioural performance and grey matter volume were identified after correcting for multiple comparisons over the whole brain volume. Restricting analyses to the pre-specified anatomical volumes of interest, performance on both ASA tests was significantly associated ($P < 0.05$) with grey matter volume in left posterior superior temporal gyrus and in posterior cingulate gyrus. In addition, performance on ASA-grouping was significantly associated ($P < 0.05$) with grey matter volume in right posterior superior temporal gyrus.

Discussion

Here we have demonstrated that clinically typical Alzheimer's disease is associated with impairments of ASA. The present evidence suggests that Alzheimer's disease is associated with a primary and generic disruption of ASA relevant to the processing of both verbal and non-verbal sounds. Our findings provide a basis for understanding deficits in processing verbal information streams shown by patients with Alzheimer's disease in previous work (Gates *et al.*, 1996, 2002, 2008, 2011). Impairments of ASA here were not attributable to disease duration or general cognitive executive performance, consistent with a relatively specific disorder of auditory

cognition. Further, impairments were not attributable to simpler auditory perceptual or task factors, suggesting that the deficit in Alzheimer's disease affects a level of complex auditory information processing that is more specifically relevant to the analysis of auditory scenes. Further, in the Alzheimer's disease group, the two ASA operations assessed (auditory object segregation and grouping) were associated with comparable profiles of impairment and neuropsychological associations; the behavioural data therefore suggest that sub-processes of ASA may (at least partially) share neural resources that are vulnerable to the pathological process in Alzheimer's disease. This conclusion is supported by neuroanatomical (voxel-based morphometry) data demonstrating involvement of common posterior cortical areas in posterior superior temporal lobe and posterior cingulate in both ASA tasks.

Performance on the ASA tasks here was influenced by non-verbal working memory capacity. Working memory is likely to play a role in the integration of auditory information over time, enabling the binding (or segregation) of features into coherent object representations during ASA. The present findings are in line with previous evidence for working memory deficits (attributed to temporoparietal dysfunction) in Alzheimer's disease (Stopford *et al.*, 2007, 2010). The cognitive and anatomical organization of working memory is complex, with evidence both for modality-specific and modality-independent processing that is modulated by task (Alain *et al.*, 2008; Klemen *et al.*, 2009; Koelsch *et al.*, 2009; Protzner *et al.*, 2009; Schulze *et al.*, 2011a, b). The effects of Alzheimer's disease upon working memory in different modalities remain disputed (Huntley and Howard, 2010); however, the present findings suggest a shared basis for non-verbal working memory deficits affecting visuospatial and auditory information in Alzheimer's disease (although specific mechanisms of non-verbal auditory working memory have not been delineated). We speculate that working memory impairments may account for the disproportionate deficits exhibited during ASA grouping versus segregation by individual patients but not by healthy older control

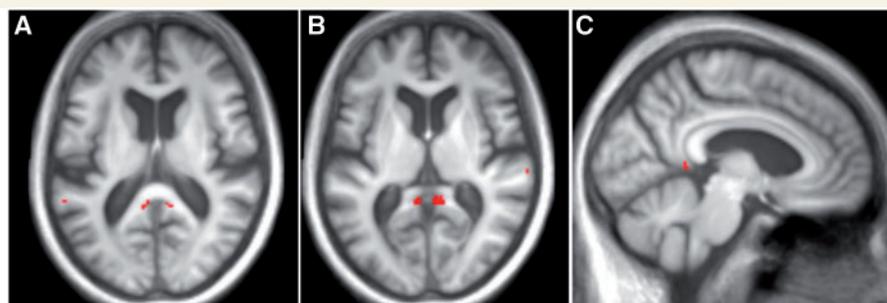


Figure 4 Statistical parametric maps of regional grey matter volume associated with ASA performance in the Alzheimer's disease cohort. The statistical parametric maps are displayed on axial (A, B) and sagittal (C) sections of the mean normalized T_1 -weighted structural brain image in DARTEL space; the right hemisphere is shown on the *right* in axial sections. Grey matter associations of ASA performance were identified in posterior cortical areas: (A) left posterior superior temporal gyrus; (B) right posterior superior temporal gyrus; (A–C) posterior cingulate gyrus. (A, C) Associations for performance on ASA-grouping, (C) associations for performance on ASA-segregation. Grey matter associations were very similar for both ASA tests within left posterior superior temporal gyrus and posterior cingulate, but were additionally found for the ASA-grouping test in right posterior superior temporal gyrus. The statistical parametric maps are based on regions for which grey matter associations were significant ($P < 0.05$) after correction for multiple comparisons over the pre-specified anatomical small volume.

subjects here (Supplementary Fig. 2): grouping processes are likely *a priori* to be particularly dependent on a capacity to track and to bind auditory information evolving over time (Bregman, 1990). Additionally, further attentional and executive mechanisms including top-down inhibitory processes are also likely to play a role in ASA: as well as binding 'target' auditory events, such mechanisms could act by suppressing interference from irrelevant 'background' sound. Involvement of these further processes would be consistent with the executive deficits exhibited by the present Alzheimer's disease group on general neuropsychological assessment (Table 1). Taken together, the present data can be interpreted in the framework of interacting 'bottom-up' perceptual and 'top-down' executive (in particular, non-verbal working memory) factors during ASA, in accord with previous evidence (Schönwiesner *et al.*, 2007; Leech *et al.*, 2009; Fishman and Steinschneider, 2010). While we have not presented evidence for a specific effect of bottom-up factors here, an adequate exploration of this issue would require the direct manipulation of acoustic properties and sound categories as well as contextual and attentional factors.

The voxel-based morphometry analysis here identified neuro-anatomical associations of ASA performance in bihemispheric posterior cortical areas including the posterior superior temporal lobes and posterior cingulate. These areas are likely to constitute a brain network mediating distinct sub-processes underpinning ASA. Previous functional imaging work has shown that the temporoparietal junction and adjacent auditory cortices are engaged during ASA tasks including dual stream processing (Deike *et al.*, 2004, 2010; Cusack *et al.*, 2005; Gutschalk *et al.*, 2007; Schönwiesner *et al.*, 2007; Snyder and Alain, 2007; Wilson *et al.*, 2007; Schadwinkel and Gutschalk, 2010; Smith *et al.*, 2010). Further, it has been proposed that the deconvolution of auditory scenes into constituent sound objects (a core operation in ASA) is based upon the matching of incoming sound mixtures to stored perceptual sound object representations or 'auditory templates' (Griffiths and Warren, 2002). The posterior superior temporal lobe is a leading candidate for the instantiation of such a template-matching process, and this region has been widely implicated in various processes directly relevant to ASA, including the tracking of auditory information streams (Deike *et al.*, 2004, 2010; Gutschalk *et al.*, 2007; Wilson *et al.*, 2007; Wong *et al.*, 2008; Overath *et al.*, 2010; Smith *et al.*, 2010; Teki *et al.*, 2011), the binding of auditory sequences (Gaab *et al.*, 2003), and the automatic detection of auditory events (Celsis *et al.*, 1999). Furthermore, evidence from focal lesion work suggests this region may play a critical role in tracking information in the auditory environment (Ducommun *et al.*, 2004). The posterior cingulate has also been linked with processes relating to ASA, in particular the integration of multimodal sensory information with behavioural goals and outputs, and with subjective states including sensory imagery (Sieroka *et al.*, 2003; Laurens *et al.*, 2005; Lockwood *et al.*, 2008; Sadaghiani *et al.*, 2009; Daselaar *et al.*, 2010; Hunter *et al.*, 2010). Furthermore, this region is a core component of the 'default mode' cerebral network linking hippocampi and mesial temporal cortex with parietal lobe cortices via limbic projection pathways, which sustains early and relatively selective damage in Alzheimer's disease (Buckner *et al.*, 2009; Seeley *et al.*, 2009; Zhou *et al.*, 2010). Involvement of the posterior

cingulate in ASA is therefore of particular interest for the broader insights it may hold into Alzheimer's disease pathophysiology.

The present findings have both clinical and neurobiological implications. Clinically, the characterization of an ASA deficit, which could potentially contribute to a spectrum of verbal and non-verbal auditory dysfunction, provides insight into an important class of symptoms in Alzheimer's disease. In patients' daily lives, this ASA deficit is perhaps most likely to manifest as difficulty understanding and following speech in the presence of extraneous noise, but could in principle affect the detection and tracking of other kinds of complex sounds (for, example salient environmental noises or music involving more than one instrumental line) and the localization of sounds in space (Smith *et al.*, 2010). It is likely that such symptoms are under-recognized in Alzheimer's disease or perhaps ascribed to deficits of memory, attention or peripheral hearing. However, the central auditory disorder identified here, while it is unlikely to benefit from amplification strategies such as hearing aids, might be managed by improved awareness and (where feasible) modification of the acoustic environment. Beyond these practical management implications, the present findings raise the possibility that improved characterization of ASA deficits might contribute to the clinical diagnosis of Alzheimer's disease. Previous work has suggested that central auditory deficits may emerge relatively early in the evolution of Alzheimer's disease (Gates *et al.*, 1996, 2002, 2008, 2011; Golob *et al.*, 2007, 2009); however, the patients with Alzheimer's disease described here had well established clinical disease, and further longitudinal investigations involving patients at earlier disease stages are required. From a neurobiological perspective, ASA provides a novel paradigm with which to address the cortical mechanisms of Alzheimer's disease. In particular, the present evidence suggests that ASA may provide a window on the operation of the core default mode network in Alzheimer's disease and the mechanisms by which this network interacts with incoming sensory information in relation to specific behavioural goals.

There are important caveats on the interpretation of this study. In particular, caution is needed in generalizing from these findings to the wider population of patients with Alzheimer's disease. It is increasingly recognized that Alzheimer's disease is a heterogeneous entity (Cummings, 2000; Alladi *et al.*, 2007; Snowden *et al.*, 2007; Stopford *et al.*, 2007, 2008, 2010), and this heterogeneity may be at least partly stratified by age (Stopford *et al.*, 2010); the current Alzheimer's disease cohort represents relatively young patients recruited via a specialist centre. The relative prominence of working memory deficits may vary among clinical subgroups of patients with Alzheimer's disease (Stopford *et al.*, 2010), while the effects of age and other clinical factors on central auditory function in Alzheimer's disease have not been systematically explored. Taking these caveats into account, our findings suggest that generic ASA processes are impaired in a cohort of patients with a clinically typical Alzheimer's disease syndrome, and suggest a programme for further work. Detailed characterization of ASA mechanisms and exploration of bottom-up perceptual (including spatial), top-down, and mnemonic factors that modulate ASA will require both neuropsychological and neuroimaging approaches, and in particular, the application of structural and functional connectivity methods to delineate the distributed neural networks that

are likely to mediate ASA. In order to realize the clinical potential of these findings, future studies should address the specificity of the ASA disorder for Alzheimer's disease versus other dementias, and the longitudinal evolution of auditory dysfunction in relation to other symptoms. Finally, it will be particularly important to evaluate the present evidence in larger populations of patients with Alzheimer's disease, including older patients and those with variant syndromes.

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Supplementary material

Supplementary material is available at *Brain* online.

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