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Processing of linguistic deixis in people with schizophrenia, with and without auditory verbal hallucinations

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ABSTRACT

Auditory verbal hallucinations (AVH) are a key symptom of schizophrenia (SZ) defined by anomalous perception of speech. Anomalies of processing external speech stimuli have also been reported in people with AVH, but it is unexplored which specific dimensions of language are processed differently. Using a speech perception task (passive listening), we here targeted the processing of deixis, a key dimension of language governing the contextual anchoring of speech in interpersonal context. We designed naturalistic speech stimuli that were either non-personal and fact-reporting ('low-deixis' condition), or else involved rich deictic devices such as the grammatical first and second persons, direct questions, and vocatives ('high-deixis'). We asked whether neural correlates of deixis obtained with fMRI would distinguish patients with and without frequent hallucinations (AVH + vs AVH−) from controls and each other. Results showed that high-deixis relative to low-deixis was associated with clusters of increased activation in the bilateral middle temporal gyri extending into the temporal poles and the inferior parietal cortex, in all groups. The AVH + and AVH− groups did not differ. When unifying them, the SZ group as a whole showed altered activity in the precuneus, midline regions and inferior parietal cortex. These results fail to confirm deictic processing anomalies specific to patients with AVH, but reveal such anomalies across SZ. Hypoactivation of this network may relate to a cognitive mechanism for attributing and anchoring thought and referential speech content in context.

1. Introduction

Disorganized and impoverished forms of language are of central clinical importance in schizophrenia (SZ) (Palaniyappan, 2021) and arguably form part of a 'core deficit' in it, relating to persisting impairments in cognition and social and role functioning (Rathnaiah et al., 2020). Specific forms of language dysfunction also characterize criterial symptoms of SZ, such as the disorganized speech of formal thought disorder (McKenna and Oh, 2005) or the anomalous perception of speech in the absence of an auditory stimulus in auditory verbal hallucinations (AVH), one of the most commonly occurring symptoms in psychosis (McCarthy-Jones, 2021). Previous neuroimaging studies of language anomalies in AVH have particularly sought to understand the role of auditory cortex in AVH, given that AVH phenomenologically

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resemble ordinary auditory speech perception in terms of perceptual qualities like volume, emotional valence, and timbre. A number of studies have found increased activation in cortical areas related to auditory and speech perception during the experience of AVH compared to alternating non-hallucinating periods (Dierks et al., 1999; Shergill et al., 2000; Lennox et al., 2000; Kompus et al., 2011). However, a recent rigorous study found no evidence of such hyper-excitability in auditory cortex, while activations in language regions did relate to AVH (Fuentes-Claramonte et al., 2021). Other studies have reported hyper-coupling (coordinated hyperactivity) across the fronto-temporal language network (Lavigne et al., 2015), which was not seen with non-auditory related tasks (i.e. inner thought generation, and a non-auditory verbal oddball perception task; see Lavigne & Woodward, 2018).

While all of these studies have analysed language at a broad perceptual or a network level, we aimed to target a specific dimension of its internal organization in a hypothesis-driven fashion here. This was the 'deictic' aspect of linguistic organization, which mediates the anchoring of speech in a context of interpersonal language use. Before any thought content expressed in speech can be fully interpreted, it needs to be related to a thinker (who is thinking it) and a context (to whom is it addressed, and what it is about). For example, the sentence *I love this*, out of context, only tells us that some person, X, loves some object or event, Y. Only when witnessing this sentence as an utterance in a context and resolving the reference of its deictic devices (*I*, *this*, and the tense on the verb), X can be identified as the *speaker* of that utterance, while Y will be identifiable from the context of the speech act itself, and the temporal location can be set to a time simultaneous to the speech event. After these parameters are fixed, the thought expressed is contextually anchored and we can determine and relate to what was said. Person deixis as encoded in the grammatical first and second persons is a key element of such anchoring. In all human languages, every noun phrase (NP) is either marked for the first or second grammatical persons (as e.g. encoded in the pronouns 'I' and 'you'), or else unmarked for person – i.e. neither the speaker nor addressee are referenced, but a third person or object (*he*, *she*, *it*, *that man*) (Hinzen & Sheehan, 2015).

Deictic anchoring and person deixis in particular relate to several key phenomenological aspects of AVH. In particular, speech is not merely nonveridically perceived in AVH, but also mistakenly anchored in the context, insofar as it tends to be attributed by hallucinators to a person speaking (such as a dead relative or God). Such evidence for a mistaken anchoring of speech in context is not prominently reported in the speech perception of people with SZ without AVH. Second, hallucinated speech in SZ is more than merely an atypical perception of speech, but often involves listening to conversations about, or directed to, the voice hearer (McCarthy-Jones, 2021). Such conversations by their nature (and unlike news reports, say) involve a rich use of deictic elements of grammar. Third, there are direct findings of anomalous distributions of the three grammatical persons in word-by-word transcriptions of hallucinated voice talk, such as an underuse of the grammatical first person in relation to the second and third persons (Tovar et al., 2019a).

Beyond AVH, person deixis may also matter to symptoms and cognitive aspects in SZ more broadly. Thus, where the first and second grammatical persons are used, not merely some external events will be referenced (e.g. *Snow is white*; *The police came*), but the speaker's own thoughts *about* them will typically also be expressed or asked for (e.g. *I like this*; *I didn't know the police was here*; *Do you agree?*; *Can you hear me?*). Use of person deixis in grammar therefore connects to the broader issue of representing mental states (one's own and those of others), and hence indirectly to 'theory of mind', which is pervasively impaired in SZ (Bora et al., 2009; Sprong et al., 2007). In turn, Crow (2010) argued that AVH along with other symptoms of SZ involve a disturbance of the 'deictic frame', in which all thought and speech take place: e.g., internal thoughts anchored in the self (first person) are heard as spoken out loud, speech is not merely heard but mis-attributed to a person who is not speaking, or speech is mis-perceived as being directed at the listener (e.g. the presenter on TV is talking to 'me'). Supporting a similar idea, Hinzen et al. (2016) suggest that a typical delusion such as the incontrovertible certainty of a patient expressed as *I am Jesus (Christ)*, also reflects a 'deictic confusion': the speaker loses a sense of his deictic location in interpersonal space, mistaking a third-person description (e.g., 'Jesus') as an identifying first person feature. Interestingly, clinical examples of delusions typically involve the grammatical first Person (e.g., *I came to Earth in a cosmic bubble*, but not *Angela Merkel is the president of the US*). Further in line with the concept of problems of deictic anchoring in SZ, Tovar et al. (2019b) found pervasive anomalies of deixis in thought-disordered speech, relating spatiotemporal anchoring more generally (e.g. patients failing to know where they are, how long they have been in a certain place, or anomalous vagueness in place reference, e.g. a patient saying 'I was born around here, in this world'). Outside of the narrow dimension of deixis, referential anomalies in a broader sense have formed a cornerstone in linguistic analyses of spontaneous speech in SZ, where such anomalies are aggravated with higher levels of formal thought disorder (Cokal et al., 2018; Sevilla et al., 2018).

The aim of the present study was to subject the deictic dimension of language to a first systematic study, using fMRI at a whole-brain level. We predicted that, although anomalies of deictic processing might characterize SZ as a whole, such anomalies might be particularly pronounced in patients with AVH when compared patients without AVH, and relate to regions of the language network. Due to a lack of previous targeted studies, our study was exploratory. Some previous work, however, has targeted aspects of cognition broadly related to deixis, such as self- versus non-self-related processing. Such processing clearly relates to the use of grammatical person, although the self- versus non-self-distinction does not specifically relate to *speech* acts and their participants. Previous fMRI studies of such self-related cognitive processing have thus used tasks such as judging whether particular personality traits apply to oneself or others (Lou et al. 2004), self-reflective consciousness during rest (Cavanna & Trimble, 2006), or spatial cognition (Vogeley et al. 2004). In such tasks, the precuneus in the medial parietal lobe has been of special interest, which could therefore relate to deictic processing as well, specifically the embedding of the self in conversational space. Vogeley & Fink (2003) specifically suggest that the medial parietal and posterior cingulate cortex are part of a network involved in assigning a 'first-person perspective' (the viewpoint of the observing self). The precuneus jointly with the right anterior insula also formed two regions of interest in what is to our knowledge the only fMRI study to date that directly targeted person deixis in grammar: Mizuno et al. (2011), who specifically investigated the neural basis of 'deictic shifts', which the authors define as 'updating the anchoring site of an utterance', or 'shifting the relationship between an utterance-generating speaker and a referred-to listener' (ibid., p.2423). In a region-of-interest analysis, the authors found a reliable increase of functional connectivity between the precuneus and anterior insula in a neurotypical adult group when the questions asked involved personal pronouns, but not when involving proper names of the participants. This effect was absent in a comparison group with autism spectrum disorder (ASD), where 'pronoun reversals' (second or third person replaced for where first person would be expected) have been a classical finding since Kanner (1943).

Apart from the precuneus, the inferior parietal lobe is of special interest with regards to deixis. This is because deixis does not primarily relate to lexical-conceptual aspects of semantic processing along the 'ventral' route, connecting the superior and middle temporal lobes to inferior-frontal regions (Hickok & Poeppel, 2007). This is evident from the fact that personal or deictic pronouns characteristically lack any such lexical-conceptual content, containing no lexical-descriptive information of their referents at all. Deixis thus serves to isolate a *referential* from a *conceptual* dimension of linguistic semantics, a distinction recently stressed by Lau (2021) (see also Jefferies et al., 2019, for a related distinction). Lau specifically argues for the temporo-parietal junction and the angular gyrus (AG) to be involved in 'referential indexing', the function of creating indices for individuals and events referenced in a sentence, to which new conceptual properties can then be bound as a narrative progresses or an event unfolds. The AG has also recently been hypothesized to relate to the embedding of complex events in time and context as required for episodic memory (Humphreys et al., 2021). Rather than to semantic knowledge as such, that is, the AG may mediate the anchoring of combinatorial meaning in time and context (Jefferies et al., 2019). Linguistic studies have also found activations of the AG in studies comparing the processing of connected discourse to the processing of unrelated sentences, phrases, or words (Fletcher et al., 1995; Homae et al., 2003; Xu et al., 2005; Ferstl et al., 2008; Fedorenko et al., 2012; Babajani-Feremi, 2017). What distinguishes sentences from word lists or unrelated phrases is not lexical-conceptual but referential meaning – meaning interpretable as true or false and linked to a (discourse-) context. The AG and inferior parietal lobe more broadly therefore formed a specific region of interest in the present study as well.

In sum, in this study we aimed to launch a first whole-brain analysis targeting the processing of the deictic dimension of language in both neurotypical people and those with SZ. Given the linguistic specificity of the phenomenon targeted here, we predicted that activations in regions within the canonical language network would index deictic processing, specifically including inferior parietal regions; but that, outside of the canonical language network, the precuneus could mediate deictic processing in language as well. We also aimed to put to an empirical test the question of whether anomalies of deictic processing are specific to patients with AVH, as compared to those without.

2. Methods

2.1. Participants

The patient sample consisted of 46 patients meeting DSM-5 criteria for schizophrenia or schizoaffective disorder, recruited from four psychiatric hospitals in Barcelona (Benito Menni CASM, Hospital Sagrat Cor de Martorell, Hospital de Sant Rafael, Hospital Mare de Déu de la Mercè). Diagnosis was established through clinical interview and review of case notes. Patients were excluded if they (a) were younger than 18 or older than 70, (b) had a history of brain trauma or neurological disease or (c) had shown alcohol/substance abuse/dependence within the 12 months prior to participation. Patients with a current IQ < 70 or who had received electroconvulsive therapy in the past 6 months were also excluded. All patients were taking antipsychotic medication.

The patients were prospectively recruited on the basis of having frequent (AVH +) or no (AVH−) current auditory hallucinations. The AVH + patients experienced at least daily AVH which in many cases were continuous or nearly continuous. Patients included in the AVH− group reported not having experienced AVH for at least six months.

Healthy controls were recruited from non-clinical staff working in the hospitals, their relatives and acquaintances, plus independent sources in the community. They met the same exclusion criteria as the patients and they were also interviewed using the SCID (Structured Clinical Interview for DSM-5, First et al. 2015) to exclude current and past psychiatric disorders. They were questioned and also excluded if they reported a history of treatment with psychotropic medication beyond non-habitual use of night sedation or if they reported a history of psychiatric disorder in a first-degree relative.

The three groups were selected to be matched for age, sex and estimated IQ (premorbid IQ in the patients). This latter was measured using the Word Accentuation Test (Test de Acentuación de Palabras, TAP; Del Ser et al. 1997; Gomar et al. 2011), which requires the pronunciation of low-frequency Spanish words, whose accents have been removed. All participants were right-handed and were native or fluent Spanish speakers.

All participants gave written informed consent prior to participation. All the study procedures complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Healthy controls received a gift-card for their participation in the study.

2.2. Clinical and cognitive assessment

AVH severity was assessed with the Psychotic Symptom Rating Scale, auditory hallucinations subscale (PSYRATS-H) (Haddock et al.,1999). This subscale consists of a semi-structured interview with 11 items referring to frequency, duration, controllability, loudness, location; severity and intensity of distress; amount and degree of negative content; beliefs about the origin of voices; and disruption caused by the AVHs. To get a more accurate measurement of hallucination frequency, candidates were asked to remain silent in a quiet environment for 5 min and tap on the table every time they heard a voice.

The PANSS scale (Kay et al., 1987) was used to assess other symptoms. Clinical severity was additionally assessed with the Clinical Global Impression (CGI, Haro et al. 2003) and the Global Assessment of Functioning (GAF) scales. Current IQ was estimated using four subtests from the WAIS-III battery (Vocabulary, Similarities, Matrix reasoning and Block design). All assessments took place within one week from the scanning session.

2.3. Deictic distinctions task

During scanning, participants performed a listening task with auditory linguistic stimuli. Two conditions, low- and high-deixis, were alternated in a block-design fashion. In the 'low-deixis' condition, participants heard speech excerpts in the form of short narratives that were impersonal and fact-stating and exclusively used the grammatical third person in any of the noun phrases used. Narrative excerpts were adapted from alternative versions of the prose recall subtest of the Rivermead Behavioral Memory Test (RBMT, Kurtz 2018) and the logical memory subtest of the Wechsler Memory Scale (WMS-III, Wechsler 1997). The original stimuli and their translation can be found in the Supplementary Information. To make this low-deixis condition as similar as possible to the high-deixis condition, and given the phenomenology of AVH in general, two female speakers took conversational turns in describing the facts or events in question, yet they did not interact with or addressed each other. In the 'high-deixis' condition, stimuli consisted of short dialogues between the same two speakers covering the same mundane topics and vocabulary, but the speakers now interacted linguistically with each other, using the grammatical first and second Persons to refer to themselves and address their interlocutor. Moreover, they occasionally spoke directly to the listener (once per block) as well, with phrases such as 'And you, who are listening, what do you think?', thus covering the full three-fold deictic frame of a conversation. Stimuli across the two conditions did not differ in syntactic complexity viewed through the proxy of the rate of embedded clauses (Mann-Whitney U test = -1.938, $p = 0.427$).

Six blocks of each condition were presented in alternating order, lasting 28 s each and separated by 14 s baseline periods in which only white noise was presented. Stimuli were delivered through MRI-compatible headphones (VisuaStim Digital, Resonance Technology, Northridge, CA, USA). To maintain visual stimulation constant and similar for all participants, the task was performed with eyes open while looking at a gray blank screen shown through MRI-compatible goggles (VisuaStim Digital).

Participants were instructed to remain silent and listen carefully to the recordings during the task. To ensure they paid attention during the task, a brief questionnaire was administered immediately after the task about the topics covered in the dialogues and narratives. Participants also self-reported their level of attention and, in the case of AVH + patients, the frequency of hallucinations during the task. Participants who reported not paying attention or were unable to identify the topics covered in the task (as defined by making 2 + mistakes in response to the

6 yes/no questions) were excluded from the analyses.

Immediately before the scanning session, participants were given task instructions and were shown a practice example of a high-deixis and a low-deixis excerpt, which was not subsequently used in the scanner.

2.4. Image acquisition

Images were acquired with a 3 T Philips Ingenia scanner (Philips Medical Systems, Best, The Netherlands). Functional data were acquired using a T2*-weighted echo-planar imaging (EPI) sequence with 257 volumes and the following acquisition parameters: TR = 2000 ms, TE = 30 ms, flip angle = 70°, in-plane resolution = 3.5 × 3.5 mm, FOV = 238 × 245 mm, slice thickness = 3.5 mm, inter-slice gap = 0.75 mm. Slices (32 per volume) were acquired with an interleaved order parallel to the AC-PC plane. We also acquired a high-resolution anatomical volume with a FFE (Fast Field Echo) sequence for anatomical reference and inspection (TR = 9.90 ms; TE = 4.60 ms; Flip angle = 8°; voxel size = 1 × 1 mm; slice thickness = 1 mm; slice number = 180; FOV = 240 mm).

2.5. Image pre-processing and analysis

Preprocessing and analysis were carried out with the FEAT module included in the FSL (FMRIB Software Library) software (Smith et al., 2004). The first 10 s (5 volumes) of the sequence, corresponding to signal stabilization, were discarded. Preprocessing included motion correction (using the MCFLIRT algorithm), co-registration and normalization to a common stereotactic space (MNI, Montreal Neurological Institute template). For accurate registration, a two-step process was used. First, brain extraction was applied to the structural image, and the functional sequence was registered to it. Then the structural image was registered to the standard template. These two transformations were used to finally register the functional sequence to the standard space. Before group analyses, normalized images were spatially filtered with a Gaussian filter (FWHM = 5 mm). To minimize unwanted movement-related effects, individuals with an estimated maximum absolute movement > 3.0 mm or an average absolute movement > 0.3 mm were excluded from the study.

Statistical analysis was performed by means of a General Linear Model (GLM) approach. Separate regressors were defined for the low-deixis and high-deixis conditions (white noise periods were not modelled and thus acted as the implicit baseline). Motion parameters obtained from realignment were also included as nuisance covariates. GLMs were fitted to generate individual activation maps for the contrast of interest, which was high-deixis > low-deixis (this contrast shows the increase in activation in response to increased deictic load). Additional contrasts were generated for each condition against the low-level baseline. Second level (group) analyses were performed within the FEAT module by means of mixed-effects GLMs (Beckmann, Jenkinson, & Smith, 2003). First, we explored group differences with a one-way ANOVA to compare the three groups (AVH+, AVH− and HC). After that, planned comparisons were performed with two-sample t-tests to compare the AVH + vs. AVH− groups, and the whole SZ group (combining the two patient samples) vs. HC. Additionally, one-sample t-tests were used to generate mean activation maps for each group (see Supplementary Information). All statistical tests were carried out with a $p < 0.05$ FWE-corrected at the cluster level using Gaussian random field methods, with a threshold of $z > 3.1$ ($p < 0.001$) to define the initial set of clusters. In all analyses, sex, age and pre-morbid IQ were used as covariates of non-interest.

3. Results

3.1. Demographic and clinical data

From an initial sample of 30 AVH + patients recruited, 4 did not complete scanning and 3 more were excluded due to excessive head motion (2) and substance use (1), leaving 23 patients to be included in the analyses. From an initial sample of 37 AVH− patients, 5 did not complete scanning and 6 more were excluded due to excessive motion (2), substance abuse/dependence (1), poor performance in the post-task questionnaire (1) and IQ below 70 (1). An additional patient was excluded due to not being completely free from AVH. Of the remaining 27 AVH− patients, it was possible to match 23 with the AVH + group on demographic characteristics. From an initial sample of 31 healthy controls, one did not complete scanning, and five more were excluded due to personal or family history of psychiatric disorder (3), motion (1) and incidental MRI findings (1), leaving a total of 25 participants to be included in analyses.

Demographic and clinical data of the final samples are shown in Table 1. Given the differences in sex proportion and age between the patient groups, we included sex, age and pre-morbid IQ as covariates in all imaging analyses. For current IQ, significant differences were found between healthy controls and AVH+ ($p = 0.001$) and at trend-level with AVH− ($p = 0.056$), but no significant differences were observed between the two patient groups ($p = 0.169$). From the 23 AVH + patients,

Table 1
Demographic and clinical data for the schizophrenia patients, divided into those with and without auditory verbal hallucinations (AVH + vs. AVH−).

	HC	AVH+	AVH−	Differences
Sex (M/F)	18/7	20/3	13/10	$\chi^2 = 5.27$, $p = 0.072$
Age	39.8 (14.08) Range = 20–64	40.09 (12.96) Range = 19–66	46.17 (7.88) Range = 32–62	$F = 2.10$, $p = 0.131$
Pre-morbid IQ	101.17 (9.91) Range = 71–114	98.39 (9.6) Range = 73–116	102.57 (8.29) Range = 85–114	$F = 1.16$, $p = 0.321$
Current IQ	108 (18.71) Range = 75–137	92.09 (13.76) Range = 70–121	98.68 (11.83) Range = 76–123	$F = 5.99$, $p = 0.004$
PSYRATS-H		24.91 (7.32) Range = Range = 11–39	0.00 (0.00)	$t = 16.32$, $p < 0.001$
PANSS Total		63.70 (15.26) Range = 43–98	53.00 (11.91) Range = 35–74	$t = 2.65$, $p = 0.011$
PANSS Positive		18.22 (5.78) Range = 10–35	11.83 (4.98) Range = 7–24	$t = 4.02$, $p < 0.001$
PANSS Negative		18.04 (6.81) Range = 8–34	16.48 (5.16) Range = 10–31	$t = 0.88$, $p = 0.385$
PANSS General		27.43 (7.81) Range = 16–50	24.70 (6.44) Range = 16–39	$t = 1.30$, $p = 0.201$
GAF		45.04 (14.68) Range = 25–70	53.65 (12.18) Range = 40–81	$t = 2.10$, $p = 0.042$
CGI		4.52 (0.85) Range = 3–6	3.80 (1.11) Range = 2–5	$t = 2.38$, $p = 0.023$
Illness duration		15.83 (10.79) Range = 1–32	20.95 (9.65) Range = 3–37	$t = 1.64$, $p = 0.108$
Treatment (mg/day in chlorpromazine equivalents)		549.81 (272.01) Range = 200–1187.5	533.69 (386.26) Range = 100–1716.67	$t = 0.16$, $p = 0.877$

Abbreviations: IQ: Intelligence quotient; PSYRATS-H = Psychotic Symptom Rating Scale, auditory hallucinations subscale (Haddock et al.,1999); CGI: Clinical Global Impression (Haro et al. 2003); GAF (Global Assessment of Functioning); PANSS: Positive and Negative Symptoms Scale.

3 had primary education, 13 secondary, 3 finished high school or professional training, 3 had undergraduate university studies and 1 had finished a college degree. From the 23 AVH−, 2 had primary education, 11 secondary, 6 high school or professional training, 2 had undergraduate studies and 5 had finished a college degree. From the 25 controls, 4 had secondary studies, 8 high school or professional training, 13 undergraduate studies and 1 had finished a college degree.

3.2. High- vs. low-deixis

To identify brain regions specifically involved in processing deixis, we examined the high > low-deixis contrast. The ANOVA showed a cluster of significant differences in the left precuneus (MNI coordinates $\times$ = -8, y = -54, z = 26; z = 3.74, cluster size = 145 voxels, p = 0.01; Fig. 1A). Planned comparisons showed no differences between the AVH + and AVH− groups. However, the combined patient group showed regions of significant hypoactivation relative to healthy controls. Description of the activation maps for each subgroup can be found in the Supplementary Information.

Listening to speech in the high-deixis condition relative to low-deixis was associated, in the HC group, with clusters of activation in the bilateral middle temporal gyri, extending into the temporal poles and the inferior parietal cortex, angular and supramarginal gyrus. Activation was also observed in the lateral frontal cortex bilaterally, encompassing the DLPFC and inferior frontal cortex and extending into the anterior insula, the superior medial prefrontal cortex and pre-SMA, the posterior cingulate and precuneus, basal ganglia and thalamus, regions of the midbrain and cerebellum (see Table 2 and Fig. 1B).

The activation pattern was highly similar in the whole SZ group, but activations appeared less marked in midline regions and inferior parietal cortex in this group (Table 2, Fig. 1C). Group comparison revealed reduced activation in the patients in the posterior cingulate cortex/precuneus, the bilateral angular/supramarginal gyrus, the anterior cingulate cortex, the superior and middle frontal gyrus and the midbrain (Table 2, Fig. 1D). No regions showed increased activity in patients relative to controls. To better interpret these differences, we explored the Low > Baseline and High > Baseline contrasts in the healthy subjects and the combined SZ group. Except for the midbrain cluster, the regions of reduced activation were all in areas of deactivation in Low > Baseline and High > Baseline (see Supplementary Information). This suggests that the results actually represented a de-activation failure during the low-deixis condition rather than reduced activation during the high-deixis condition.

4. Discussion

There are three core findings to this study. First, processing anomalies of deixis affect people with SZ at large, with no differences seen between the AVH + and AVH− groups. This refutes the hypothesis that a problem of deictic anchoring might distinguish hallucinating from non-hallucinating patients, and is consistent with theoretical conceptions where a 'deictic confusion' affecting the anchoring of speech and thought in context cuts across different core symptoms including delusions, AVH and formal thought disorder (Crow, 2010; Hinzen et al., 2016; Tovar et al., 2019b). Thus, people with AVH are confused over who thinks or says what, people with formal thought disorder show difficulties in locating events in space and time, while people with delusions often do not know who they are, i.e. which identifying description (e.g. being Jesus, or having a thousand children) applies to them. Differences in deictic processing could cause such difficulties, since they mediate the anchoring of thought and speech content. Such differences clearly do not identify AVH, yet a deictic confusion leading to a misattribution of speech is only one dimension of AVH. The crucial other dimension is that, phenomenologically, speech comes to be perceived or heard. Unravelling the neural basis of this dimension of AVH may therefore prove to be key.

Second, high-deixis when compared to low-deixis invoked largest activation clusters in core perisylvian language regions including the

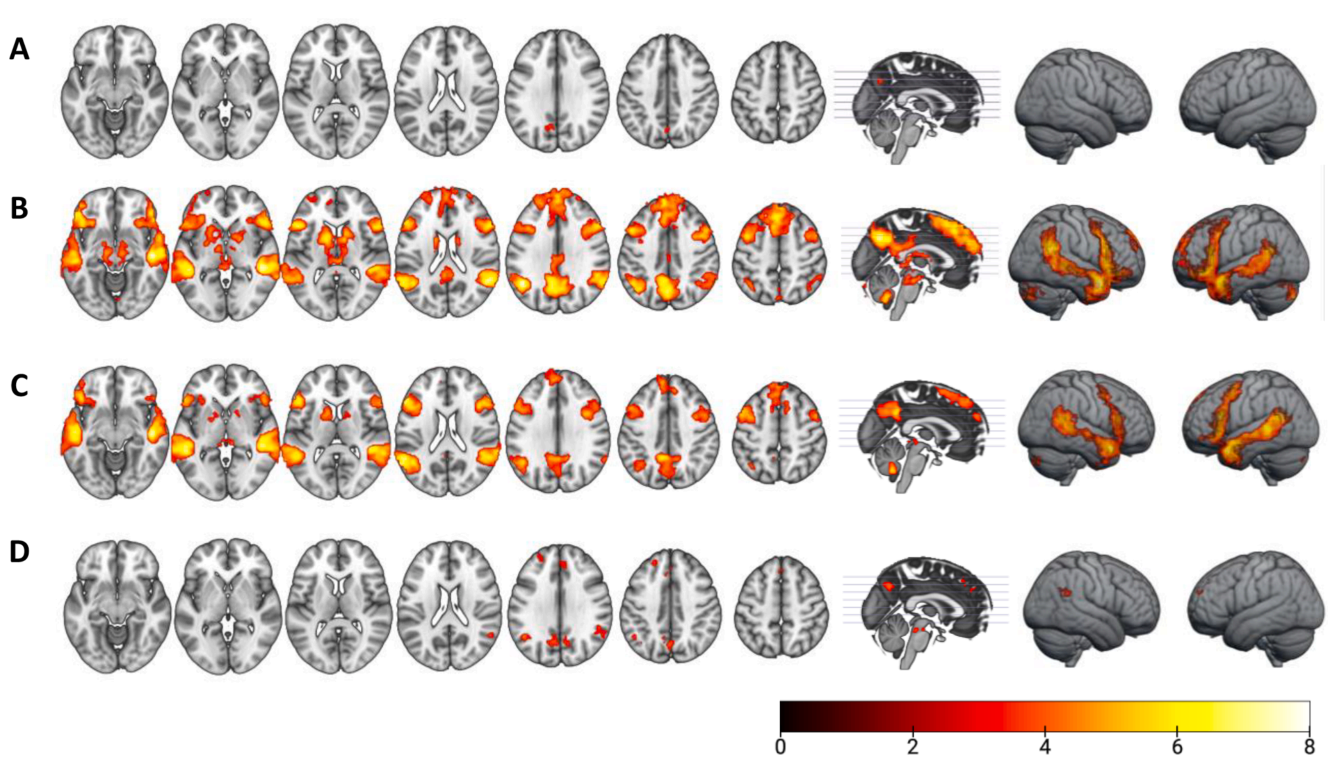

Fig. 1. Brain activation patterns in the high > low deixis contrast. A: Results from the ANOVA comparing the three groups (AVH+, AVH− and HC). B: Areas of increased activation in high > low in the healthy controls. C: Areas of increased activation in high > low in the schizophrenia patients combined. D: Areas of significant differences between the combined patient group and controls. Color bar depicts z values. Images are shown in neurological convention (right is right).

Table 2
Regions of significant activation in the high-deixis > low-deixis contrast in healthy controls and schizophrenia patients, and group differences.

Region	MNI coordinates *x*	*y*	*z*	*Z*	*k*	*p*
Controls (HC)						
Angular gyrus	−46	−56	28	8.01	21,815	<0.001
Middle temporal gyrus	−52	−26	−6	7.43		
Temporal pole	−50	10	−26	7.22		
Inferior frontal gyrus	−50	20	8	7.00		
Temporal pole	52	10	−24	8.60	10,715	<0.001
Middle temporal gyrus	50	−22	−8	8.12		
Middle temporal (posterior)	54	−54	20	7.39		
Inferior frontal gyrus	56	22	26	6.55		
Cerebellum	32	−80	−42	7.49	4674	<0.001
	−28	−82	−38	6.86		
Precuneus	−8	−56	36	7.38	3283	<0.001
Cerebellum	6	−60	−44	6.10	548	<0.001
Patients (SZ)						
Temporal pole	−46	12	−26	8.07	9780	<0.001
Middle temporal gyrus	−53	−38	4	7.35		
Inferior frontal gyrus	−54	24	20	7.14		
Middle temporal gyrus	50	−18	−10	7.72	7454	<0.001
Temporal pole	52	12	−20	7.54		
Middle temporal (posterior)	46	−38	10	6.75		
SMA	−6	12	62	5.69	2149	<0.001
Medial superior frontal gyrus	−8	54	26	5.59		
Precuneus	−6	−50	38	6.29	1484	<0.001
Cerebellum	24	−76	−38	6.27	1180	<0.001
	−20	−80	−34	6.19	787	<0.001
	2	−56	−42	5.88	363	<0.001
Caudate	−10	8	10	4.73	320	<0.001
Midbrain	4	−26	−4	4.55	157	0.007
Caudate	8	6	4	4.27	114	0.032
Controls > Patients						
Precuneus	−10	−52	26	4.24	445	<0.001
Supramarginal gyrus	52	−42	34	4.04	233	<0.001
Angular gyrus	−46	−56	30	4.47	177	0.004
ACC	6	38	32	3.87	131	0.017
Midbrain	6	−26	−16	4.28	122	0.024
Middle frontal gyrus	−26	54	26	3.84	112	0.034

SMA: Supplementary motor area; ACC: Anterior cingulate cortex.

angular gyrus (AG), the middle temporal gyrus, temporal pole, and inferior frontal cortex. Additionally, activations in the precuneus and cerebellum were seen. This is in line with our prediction of a differential response to high-deixis in the AG and precuneus, as well as, more generally, with the idea that deixis captures a core dimension of language as reflected through activations in canonical language regions. As for the AG, this region has long been depicted as a region involving high-level, supramodal integration of information in the human brain (Geschwind 1965; Binder et al., 2009). However, as noted in the introduction, several lines of research have indicated that it may be more specifically involved in the generation of meaning at a sentence and discourse level, as distinct from lexical conceptual meaning (Xu et al. 2005; Ferstl et al., 2008; Fedorenko et al., 2012; Babajani-Feremi, 2017; Lau, 2021), and that it mediates the online temporal buffering of combinatorial semantic information over time (Humphreys et al., 2021). Consistent with these findings, our findings suggest a role for the AG in the generation of referential meaning, which by its nature is both integrated with context and temporally stable, outlasting the moment in which it is produced, as the same entity is referenced again. In this way reference enables episodic memory, and it is by its nature multi-modal, as an entity referenced will always be describable under different modal perspectives and can change these over time, while remaining the same entity.

Previous fMRI studies have related the precuneus to 'self-related' cognitive processing (Lou et al., 2004; Cavanna & Trimble, 2006) and a 'first-person perspective' (Vogeley & Fink, 2003), outside of a linguistic context. The same area has been found to be a part of the 'extended' language comprehension network in studies of discourse and story comprehension (Whitney et al., 2009; Ferstl et al., 2008; Babajani-Feremi, 2017). The precuneus was also one region of interest in the only study that to our knowledge has focused on a grammatically defined deictic contrast directly (Mizuno et al., 2011), which found differences in functional connectivity in this region and in the right anterior insula in an adult autism group relative to controls. In the present whole-brain analysis, the same two regions were associated with high-vs. low-deixis in the whole sample, and in the context of our task, we may view them as part of the 'extended' language network. That network includes classical language regions such as the inferior frontal and middle temporal gyri, as well as the angular and supramarginal gyri and the temporal pole, and as Ferstl et al. (2008) note, it also shows overlaps with regions classically associated with ToM (anterior temporal lobe, temporo-parietal junction, dorsomedial prefrontal cortex: see Saxe & Kanwisher, 2003; Frith et al., 2003). Activations in the cerebellum were not predicted, and specifically located in the Crus II, which has previously been linked to the sequencing of social actions and self-related processing (van Overwalle et al., 2020). Interestingly, a functional connectivity map in Neurosynth (neurosynth.org/locations/32_-80_-42_6/) seeded in our peak coordinates in the cerebellum show a co-activation pattern with core regions of the language network also seen activated in our high > low contrast, such as the left inferior frontal gyrus, left middle temporal cortex and left inferior parietal cortex.

The third key finding of our study is that while activations in the SZ group were largely similar, differences between conditions were reduced in the SZ patients, specifically in the precuneus and inferior parietal cortex (supramarginal and angular gyri), and ACC. This highlights the significance of the inferior parietal cortex not only in relation to referential and deictic processing, but to the language profile of SZ. Current models of language in psychosis have already stressed referential function as the key dimension of interest in the SZ context (Hinzen and Rosselló, 2015; Hinzen, 2017). Referential interpretation requires context, and problems of the contextual integration of language have formed a cornerstone of psycholinguistic investigations of language processing in SZ (Ditman & Kuperberg, 2010; Ditman et al., 2011). Group differences in the precuneus were specifically located in the subregion of the precuneus identified as the 'central cognitive' one in Margulies et al. (2009), which is functionally connected to dorsolateral prefrontal, dorsomedial prefrontal, and multimodal lateral inferior parietal cortex (Luo et al., 2020; Tanglay et al., 2021), partially overlapping with regions of the Default Mode Network (DMN). The other regions of differences also overlapped with the DMN. Altered function in the precuneus could therefore indicate changes in the integration and interaction of the language and DMN networks in SZ. Reduced differences between the high- and low-deixis conditions were also found in the ACC, which has formed a key region of interest in language models of SZ for many years. An association between language disorganization and impoverishment and reduced engagement of DLPFC with the ACC has been reported in patients when performing an n-back task (Fuentes-Claramonte et al., 2020). Also, higher glutathione levels in the ACC have been found to be associated with greater levels of disorganisation in first episode schizophrenia (Pan et al., 2021).

In sum, our paradigm has provided evidence for an extended language network involved in deictic anchoring, which is further connected to regions previously identified as being involved in self-related and social cognitive processing such as the precuneus and the cerebellum. While hypoactivations in this network can be seen in SZ, possibly an indexing a mechanism underlying a range of symptoms, they do not characterize patients with AVH as compared to those without. Limitations of this study include that we did not control for potential linguistic comprehension difficulties in patients, which have been previously attested (e.g. Condray et al., 1995; Boudewyn et al., 2012), though our questionnaire indirectly addressed this issue.

5. Conclusions

This first study targeting grammatically-mediated deictic devices in language has suggested that deixis forms a part of the extended language network as previously identified in studies of discourse, and specifically that the inferior parietal cortex is a key region for the study of referential meaning viewed as partially distinct, though integrated with, lexical conceptual meaning. Moreover, while a disturbance in the generation and contextual integration of referential meaning characterizes the language profile of SZ as a whole, it is not specific to patients with AVH.

CRediT authorship contribution statement

Paola Fuentes-Claramonte: Methodology, Investigation, Data curation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Joan Soler-Vidal:** Investigation, Formal analysis, Writing – original draft, Writing – review & editing. **Pilar Salgado-Pineda:** Funding acquisition, Investigation, Writing – review & editing. **Nuria Ramiro:** Investigation, Writing – review & editing. **María Ángeles García-León:** Investigation, Data curation, Writing – review & editing. **Ramon Cano:** Investigation, Writing – review & editing. **Antonio Arévalo:** Investigation, Writing – review & editing. **Josep Munuera:** Resources, Writing – review & editing. **Francisco Portillo:** Investigation, Writing – review & editing. **Francesco Panicali:** Investigation, Writing – review & editing. **Salvador Sarró:** Investigation, Software, Writing – review & editing. **Edith Pomarol-Clotet:** Conceptualization, Investigation, Supervision, Funding acquisition, Writing – review & editing. **Peter McKenna:** Conceptualization, Supervision, Funding acquisition, Writing – review & editing. **Wolfram Hinzen:** Conceptualization, Funding acquisition, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.103007.

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