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Neuropsychological analysis of auditory verbal hallucinations

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Abstract

Recent neuropsychological studies have distinguished deficits in verbal working memory, verbal memory, and confrontation naming from other neuropsychological domains as specifically related to the severity of auditory verbal hallucinations (AVH) in schizophrenia (Gisselgard et al., 2014; Siddi et al., 2017). To extend this research, it was hypothesized that AVH severity would be related only to measures within the language domain and the test battery was augmented with the [CTOPP2 and COWAT...define?] to more comprehensively define the language processing functions most predictive of AVH. A neuropsychological test battery was administered to a group of adult patients diagnosed with schizophrenia and schizoaffective disorder (N = 30), who continued to experience AVH despite clinical treatment. Multiple regression analyses demonstrated that poorer performance on measures of verbal working memory and verbal immediate memory significantly predicted greater AVH severity. Going beyond the prior studies, it was also shown that greater impairment of semantic fluency and lesser impairment in delayed general memory were also significant predictors of AVH. Intellectual ability and executive functioning, considered as covariates, were not significant predictors and their inclusion in regression analyses did not affect the pattern of results. Lastly, when cognitive predictors were accounted for, a trend toward an effect of medication (assessed as olanzapine equivalents) emerged such that higher dose predicted less severe AVH. Taken together, better performance on measures of linguistic processes associated with verbal working memory, semantic fluency and verbal

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learning predicts less severe AVH, perhaps most consistent with limited capacity language processing models. The finding that better delayed memory predicted more severe AVH is consistent with AVH memory models suggesting that AVH are dependent upon information recalled from memory storage.

Keywords

Auditory Verbal Hallucinations Neuropsychology; Neuropsychiatry; Cognitive Functioning; Language Functions

1. Introduction

The neuropsychological deficits of schizophrenia are well characterized (Schaefer et al., 2013), but how those cognitive deficits may uniquely relate to individual schizophrenia (SZ) symptoms remains a topic of ongoing research. In taking a neuropsychological approach, the method conferring the strongest level of inference from test scores to known neural circuits involves investigation of AVH in terms of a battery of neuropsychological tests validated in the assessment of known brain dysfunction (Clark et al 2012). Initial investigations of this type revealed links between hallucination-related language tracking abnormalities in receptive language (Hoffman et al., 1999) and “lexical overactivation” in expressive language and fluency tasks (Kerns et al., 1999). Using a neuropsychological battery approach to parse the cognitive substrates of hallucinations versus delusions, hallucinations were found to be negatively correlated with performance on episodic memory tasks and delusions were unrelated to neuropsychological functions (Berenbaum et al., 2008). However, these studies relied on diverse hallucination rating scales that were not specific to auditory verbal hallucinations (AVH) making comparison between studies uncertain and perhaps underestimating the importance of language systems specific to AVH. In three recent studies, the administration of a comprehensive neuropsychological test battery was coupled with the Psychotic Symptoms Rating Scales (PSYRATS, Haddock et al., 1999), a scale specifically designed to assess the experience of ‘hearing voices.’ In the first, a sample of fifty-two patients experiencing AVH as part of first episode psychosis revealed that of multiple domains assessed, only verbal working memory measures predicted AVH severity (Gisselgard et al., 2014). More recently, Siddi et al (2017) administered a comprehensive neuropsychological test battery to groups of patients who experienced frequent AVH ($N = 29$) and patients who did not experience AVH ($N = 29$). The frequent AVH group were found to have relative deficits in set shifting and semantic fluency, the authors hypothesizing that semantic fluency was a special case of set-shifting ability and concluding that AVHs may reflect an impaired ability of patients to shift their attention away from AVH voices. Of perhaps equal importance, both studies were able to demonstrate the cognitive specificity of the relationship with AVH because functioning within other neuropsychological domains had no relevance for AVH.

The current research was similarly undertaken to use a neuropsychological test battery approach to characterize AVH-related cognitive functions. To do so, a test battery was designed to assess a broad sample of cognitive domains in a sample of SZ experiencing

AVH despite current treatment. Based upon the findings of prior studies, a particular emphasis was placed on assessment of language functioning. A multiple regression approach was employed to distinguish the independent variance in cognitive functions associated with AVH. It was hypothesized that of multiple cognitive domains, only language measures would predict AVH. It was further hypothesized that within the battery of language tests, only semantic processing measures would be associated with AVH.

2. Experimental/Materials and methods

2.1. Participants

Diagnosis was confirmed in thirty volunteers with schizophrenia and schizoaffective disorder (SZ) using the SCID-DSM-IV-TR, Patient-Version (First et al., 2002). Participants were between the ages of 18 and 60 years old with no current substance abuse or dependence (except nicotine) and no history of brain injury or other neurological disorder. All were on a stable regimen of antipsychotic medications for at least four weeks and were experiencing frequent AVH despite current clinical treatment. The University of New Mexico Human Research Protections Office (HRPO/IRB) reviewed this protocol and approved it prior to collection of any data.

2.2. Procedures

AVH severity was assessed as the Psychotic Symptom Rating Scales (PSYRATS; Haddock et al., 1999), AVH Total score. Three core neuropsychological test batteries were administered: The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph et al., 1998), the Controlled Oral Word Association Test (COWAT; Lezak 1995), and the Comprehensive Test of Phonological Processing–Second Edition (CTOPP2; Wagner et al., 2013). Neuropsychological domain scores considered as covariates included estimated WAIS-III full scale intellectual quotient (FSIQ) derived from the Wechsler Test of Adult Reading (WTAR; Holdnack 2001), an executive function score (EF) computed as the mean age-corrected standard scores for the Wisconsin Card Sorting Test: Computerized Version-4 (WCST; Psychological Assessment Resources, 2003), a perseverative errors score, the Delis-Kaplan Executive Function System, the Tower Test (Delis et al., 2001) total achievement score, and the Trail Making Test, Trails B score (Reitan 1958; Heaton et al., 2004). All measures were administered by trained technicians under the supervision of a neuropsychologist (RJT).

3. Results

One participant's data was excluded due to scores exceeding three standard deviations from the group mean, resulting in a final sample comprised of 17 males and 12 females, with a mean age of 40.3 years ($sd = 11.8$), duration of illness of 17.1 years ($sd = 11.3$) and a mean PSYRATS total AVH score of 26.46 ($sd = 5.85$). All neuropsychological domain score distributions met Shapiro-Wilk test criteria for normality. All neuropsychological subtest score distributions met Shapiro-Wilk test criteria for normality with two exceptions, the RBANS Picture Naming ($W(28) = .78$, $p = .001$; skewness = -1.68 ; kurtosis = 3.53) and List Recognition ($W(28) = .86$; $p < .001$; skewness = -1.18 ; kurtosis = $.92$) subtests were skewed

negatively in a manner indicating the presence of a ceiling effect. To characterize the cognitive characteristics of the present sample, Table 1 shows how the RBANS Index score relates to published normative data from both healthy and SZ groups.

AVH severity was considered as a dependent variable in three independent multiple regression analyses, one each for the RBANS, the COWAT, and the CTOPP2. Within each regression analysis, FSIQ, EF, age, gender, handedness (left, right), diagnosis (schizophrenia-schizoaffective) and antipsychotic medication (MED; coded as summed olanzapine equivalents for the primary and secondary antipsychotic) were tested as covariates.

In a first regression, the RBANS Immediate Memory, Visuospatial, Language, Attention, and Delayed Memory index scores were entered as predictors. The overall regression was significant ($R^2 = .44$, $p = .02$), and only the effect of Immediate Memory was significant ($\beta = -.83$, $p = .006$). When covariates were tested, a significant effect of gender emerged ($\beta = -.38$, $p = .05$) indicating that when RBANS cognitive measures were controlled for, females had lower PSYRATS total AVH scores than males. In addition, when the effect of gender was accounted for, a positive effect of Delayed Memory became significant ($\beta = .46$; $t = 2.28$, $p = .03$). There was a trend for the effect of MED ($\beta = -.31$, $t = -1.79$, $p = .08$) such that higher MED predicted lower PSYRATS total AVH score. In a second regression analysis, the COWAT Phonemic Fluency and Semantic Fluency composite scores were entered as predictors. The overall regression was significant ($R^2 = .26$, $p = .02$), and only the effect of Semantic Fluency score was significant ($\beta = -.53$, $t = -3.07$; $p = .005$). When covariates were tested a trend for the effect of MED emerged ($\beta = -.27$, $t = -1.72$, $p = .09$) indicating that higher MED predicted lower PSYRATS total AVH score. In a third regression analysis, the CTOPP2 Phonological Awareness and Phonological Memory scores were entered as predictors. The overall regression was significant ($R^2 = .23$, $p = .04$), and only the effect of Phonological Memory was significant ($\beta = -.39$, $p = .04$). [maybe not an issue, given the previous review didn't raise, but do you need to consider multiple comparisons for these?]

As measures of verbal memory (RBANS Immediate Memory), verbal working memory (CTOPP-2 Phonological Memory), and semantic fluency (COWAT Semantic Fluency) were each found to be significant predictors of AVH severity in battery-specific regression analyses, a fourth multiple regression analysis was done to determine statistical independence amongst them. The overall R^2 was significant ($R^2 = .36$, $F = 4.22$, $p = .02$), and of the predictors, only COWAT Semantic Fluency ($R^2\text{-change} = .22$, $F\text{-change} = 7.21$, $p = .01$) and CTOPP-2 Phonological Memory ($R^2\text{-change} = .12$, $F\text{-change} = 6.28$, $p = .05$) accounted for significant variance in AVH severity.

4. Discussion

Of multiple neuropsychological domains assessed, only the RBANS Immediate Memory Index, a measure of verbal learning, independently predicted AVH severity. Of the two COWAT domain scores, phonemic- and semantic-fluency, only semantic fluency score predicted AVH severity. Of the two CTOPP-2 domain scores, only Phonological Memory, a

measure of verbal working memory, predicted AVH severity. Hence, the primary hypothesis was supported, in that only neuropsychological functions within the language domain were associated with AVH [nice!]. All three were correlated with AVH such that poorer verbal functioning predicted more severe AVH. That the strength of these predictors did not change when considered in the context of intellectual ability and executive functioning cognitive covariates (IQ, EF), often found to be impaired in groups of schizophrenia patient, is further evidence of the specificity of semantic fluency, verbal working memory and verbal learning as AVH predictors.

The fourth regression analysis revealed that of the three predictors of AVH, only verbal fluency, within the expressive language domain (REF), and verbal working memory, within the receptive language domain (REF) were independent predictors of AVH. That verbal learning was secondary to processing within the working memory system is consistent with Baddeley's conceptualization of learning processes relying on preliminary processing within the phonological loop prior to information being available for memory storage (Baddeley, 2012). The two surviving AVH predictors, semantic fluency and verbal working memory, are both thought to rely on prefrontal inhibitory processing to inhibit non-relevant information from task performance (REF), and to upon rapid lexical/semantic access associated with temporo-parietal linguistic processing for successful task performance. The finding that better delayed memory performance predicted more severe AVH is perhaps consistent with memory models of AVH, in that increased access to stored information allow greater elaboration of AVH phenomenology. That increased dose of antipsychotic medication predicted less severe AVH was unexpected in this small sample, but that it was evident only after cognitive functioning was accounted for within regression equations has implications for future trials of antipsychotic medications.

The complexity of the conclusions drawn from this study was limited by small sample size and generalizability was perhaps limits by the specificity of the sample. However, the results are consistent with prior neuropsychological studies of AVH, with current theoretical models of AVH generation, and with neuroimaging studies showing abnormality in fronto-temporo-parietal networks as underlying generation of schizophrenia AVH (us, Frith, Fein, Ford, Hoffman, etc).

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Figure 1.

Table 1
RBANS Sample Index Means Relative to Published Normative Data

RBANS Index	General Population Norms (Reynolds, 1998)		Schizophrenia Norms (Wilk et al., 2004)	
	z-score	p-value	z-score	p-value
Immediate Memory Index	-2.01	p< .001	-0.05	p = .83
Visuospatial/Constructional Index	-1.74	p< .001	-0.26	p = .06
Language Index	-0.92	p< .001	0.12	p = .56
Attention Index	-1.18	p< .001	0.54	p = .01
Delayed Memory Index	-1.98	p< .001	-0.19	p = .38

Table 2
Results of the three multiple regression analyses

Analysis	Multiple Regression			
	Predictor variables	Beta	t	p-value
Regression#1	RBANS Immediate Memory Index	-.79	-3.02	.006
	RBANS Visuospatial Index	-.09	-0.57	.58
	RBANS Language Index	-.14	-0.69	.49
	RBANS Attention Index	.24	1.15	.26
	RBANS Delayed Memory Index	.30	1.50	.15
Regression#2	COWAT Phonemic Fluency	.33	1.81	.09
	COWAT Semantic Fluency	-.53	-3.07	.005
Regression#3	CTOPP2 Phonological Awareness	-.14	1.00	.45
	CTOPP2 Phonological Memory [/]	-.45	-2.47	.02

[/]Estimated composite using RBANS Digit Span + CTOPP-2 Non-word Repetition scores