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Does ketamine mimic aspects of schizophrenic speech?

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Abstract

Speech disturbances are well-known symptoms contributing to the diagnosis of schizophrenia. Subanesthetic doses of the *N*-methyl-D-aspartate (NMDA) antagonist ketamine have been reported to produce positive and negative symptoms and cognitive impairments consistent with those seen in schizophrenia. Insofar as this is true, it constitutes evidence that the NMDA system is involved in schizophrenia. It is therefore of interest to know whether ketamine produces speech disturbances like those of schizophrenia.

Quantitative computer-aided analysis of apparently normal speech can detect clinically relevant changes and differences that are not noticeable to the human observer.

Accordingly, in this study, speech samples were analysed for repetitiousness, idea density, and verb density using software developed by the authors. The samples came from two experiments, a within-subjects study of healthy volunteers given intravenous ketamine versus placebo, and a between-groups study of patients diagnosed with schizophrenia and comparable healthy controls.

Our primary hypothesis was that in both schizophrenia and ketamine, repetitiousness would increase, since perserverative speech is a well-known symptom of schizophrenia. Our secondary hypotheses were that in both schizophrenia and ketamine, idea density and verb density would decrease as indicators of cognitive impairment.

The primary hypothesis was confirmed in the schizophrenia experiment (between groups) and the ketamine experiment (within subjects).

The secondary hypotheses were disconfirmed except that in the ketamine experiment, verb density was significantly lowered. Reduced use of verbs apparently reflects a cognitive impairment of a different type than repetitiousness, and further investigation is needed to determine whether this impairment occurs in psychosis.

Keywords

ketamine, schizophrenia, *N*-methyl-D-aspartate (NMDA), speech, language, verbal behavior, perseveration, verbs, idea density

Introduction

Abnormal speech (defined as 'disorganized' speech and 'incoherence') is one of the core symptoms for diagnosing schizophrenia (Andreasen, 1979a, b; APA, 1994; Covington *et al*., 2005; McKenna and Oh, 2005). Administration of subanesthetic doses of the *N*-methyl-D-aspartate (NMDA) antagonist ketamine has been claimed to produce a condition mimicking psychotic symptoms, including disorganized speech, in healthy volunteers (Abi-Saab *et al*., 1998; Krystal *et al*., 2003). It is therefore of interest to know whether the speech disturbances in both conditions are comparable.

Quantitative language measurements as disease markers

Quantitative computer-aided analysis of apparently normal language can detect clinically relevant changes and differences that are not noticeable to the human observer. For example, Snowdon *et al*. (1996) and Kemper *et al*. (2001) were able to predict Alzheimer's disease from language samples taken more than 50 years before the onset of symptoms. Their subjects were a group of 678 elderly nuns who had written autobiographies when they joined their order, between age 20 and 25. Text samples from these autobiographies

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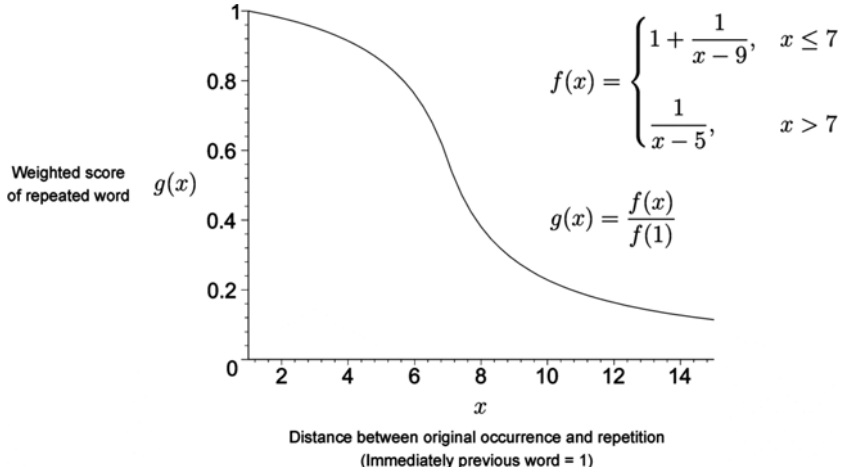

Figure 1 Sigmoid function for scoring repetitiousness.

known to involve wide-ranging cognitive impairment (Goldberg *et al*., 2003), we hypothesized that idea density would be reduced in schizophrenia and with ketamine.

Idea density is the number of propositions in a text divided by the number of words. Propositions are units of information. For example, *The big dog barks in the garden* contains three propositions: the dog is big, the dog barks, and it happens in the garden.

The term *proposition* comes from philosophical logic, in which a proposition is whatever can be true or false. In psychology, however, the criteria for identifying propositions have been shaped by empirical experiments, mainly on memory and text comprehension (Bransfor and Franks, 1971; Kintsch and Keenan, 1973; Ratcliff and McKoon, 1978; Kintsch and van Dijk, 1978; and especially Kintsch, 1974; 1988; Turner and Greene, 1978).

In English, the number of propositions in a text is almost identical to the total number of verbs (excluding all forms of *do, have* and *be*), adjectives, adverbs, prepositions, and subordinating conjunctions (but not nouns or coordinating conjunctions). Thus, idea density can be measured with part-of-speech tagging software. For this analysis, the texts were tagged with the current (2005) version of CLAWS (Garside, 1996) using its CL5 (BNC) tagset. The job of the tagger is to use both a built-in dictionary and rules of grammar to 'tag' each word as a noun, verb, adjective or other syntactic category.

We took the number of propositions (ideas) to be the number of CLAWS tags of types AJ0 (adjectives), AJC (comparative adjectives, e.g. *better*), AJS (superlative adjective), AV0 (adverb), AVP (adverbial particle), AVQ (*wh*-adverb, e.g. *why*, *when*), CJS (subordinating conjunction, e.g. *although*), PRF (the preposition *of*), PRP (prepositions other than *of*), VM0 (modal verb), VVB (lexical base verb), VVD (past tense form of lexical verb), VVG (lexical verb +*ing*), VVI (infinitive of lexical verb), VVN (past participle form of lexical verb, e.g. *taken*), and VVZ (+*s* form of lexical verb, e.g. *takes*). The verbs *do, have* and *be* were excluded, even though they sometimes express propositions, because in most cases they are auxiliary verbs, and distinguishing non-auxiliary occurrences of them would require further analysis.

Idea density was calculated as the total count of the aforementioned tags (the number of propositions) divided by the total number of words, which was obtained by counting all the tags other than punctuation marks.

Verb density Verb density is the number of verbs (lexical and modal) divided by the total number of words. Verbs are loci of syntactic and semantic complexity because they are the nexus of argument structure (subject, object, indirect object) (Jackendoff, 2002). Impairment in the use of verbs is well known in aphasia (Druks, 2002).

Since schizophrenia is known to involve simplification of syntax, probably reflecting simplification of semantics (Morice and McNicol, 1985, DeLisi, 2001), we hypothesized that idea density would be reduced in schizophrenia and with ketamine.

Note that verb density is a component of idea density; that is, verbs are one of several syntactic categories that are counted to determine idea density.

Statistical Analyses

All statistics were computed with SAS version 9 (SAS Institute, Cary, NC, USA) using PROC TTEST. The significance level threshold was set at $p = 0.05$.

Between-groups two-tailed *t*-tests were carried out to test the difference between schizophrenic patients and healthy controls. Within-subject two-tailed paired *t*-tests were done to test for the effects of ketamine.

Results

Comparisons of the measured variables in both experiments are summarized in Fig. 2. Within-subject changes for the ketamine experiment are summarized in Fig. 3.

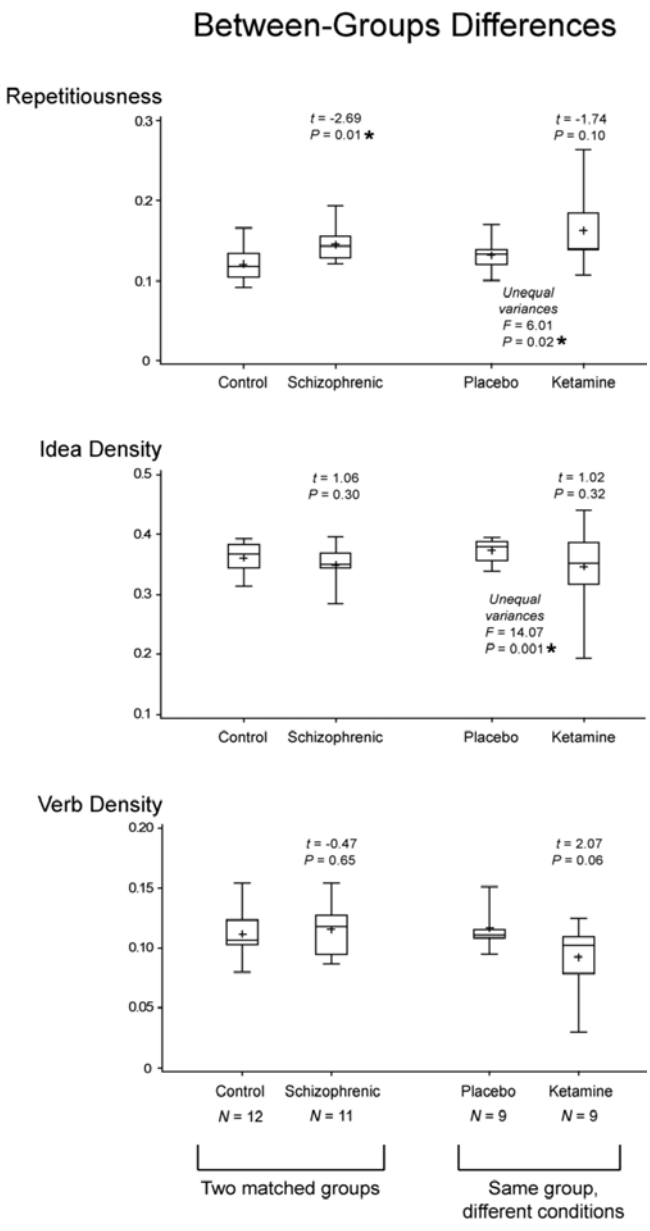

Figure 2 Comparison of measured speech characteristics between groups Box plots show minimum, quartiles, maximum, and mean (as +). Values are indicated as mean ± standard deviation.

Schizophrenia

Repetitiousness. The weighted repetition score in schizophrenic patients' speech, divided by total number of words, averaged 0.145 (±0.022 S.D.); for healthy controls, this value averaged 0.121 (±0.022 S.D.). Between-groups *t*-tests revealed that this difference was statistically significant ($t = -2.69$, df = 21, $p = 0.01$).

Idea density Schizophrenic patients' speech contained 0.349 ± 0.030 (mean ± S.D.) propositions per word, whereas healthy controls' speech contained 0.362 ± 0.026. This difference is not considered meaningful and between-groups *t*-tests revealed no statistically significant difference ($t = 1.06$, df = 21, $p = 0.30$).

Verb density The speech of schizophrenic patients and of healthy controls contained, respectively, 0.116 ± 0.020 and 0.112 ± 0.022 verbs per word. Between-groups *t*-tests revealed no statistically significant difference ($t = 0.47$, df = 21, $p = 0.64$).

Ketamine

Repetitiousness The weighted repetition score, divided by total words, averaged 0.162 (± 0.049 SD) in ketamine-influenced speech and 0.132 (± 0.020 SD) in placebo speech. The mean ± S.D. change in each subject, from placebo to ketamine, was + 0.031 ± 0.038. Within-subject paired t-tests revealed that this difference was significant ($t = 2.40$, df = 8, $p = 0.04$).

Idea density Ketamine-influenced speech on average contained 0.346 (± 0.076 S.D.) propositions per word, whereas placebo speech contained 0.373 ± 0.020 propositions per word. The means of the groups were not significantly different ($t = 1.02$, df = 16, $p = 0.33$), but the standard deviation of the ketamine group was significantly higher ($F = 14.07$, $p = 0.001$), showing that the effect of ketamine was appreciably different from subject to subject.

The mean ± S.D. change in each subject, from placebo to ketamine, was −0.027 ± 0.063. Within-subject paired *t*-tests showed that this change was not statistically significant ($t = -1.28$, df = 8, $p = 0.24$).

Verb density Ketamine-influenced speech on average contained 0.092 (± 0.030 S.D.) verbs per word, whereas placebo speech on average contained 0.117 ± 0.019 verbs per word. The mean ± S.D. change in each subject, from placebo to ketamine, was −0.024 ± 0.021. Within-subject paired *t*-tests revealed that this difference was statistically significant ($t = -2.61$, df = 8, $p = 0.03$).

Discussion

Main results

This is an initial study, with small-scale experiments, of entirely new techniques. As far as we know, this is the first demonstration of the use of computer speech analysis to detect and compare language abnormalities in schizophrenia and ketamine.

The results only partly fit our hypotheses, which were that both schizophrenia and ketamine would increase repetitiousness, reduce idea density, and reduce verb density. In fact, repetitiousness was significantly elevated in both schizophrenia and ketamine, but idea density was not significantly different, and only ketamine produced a significant drop in verb density.

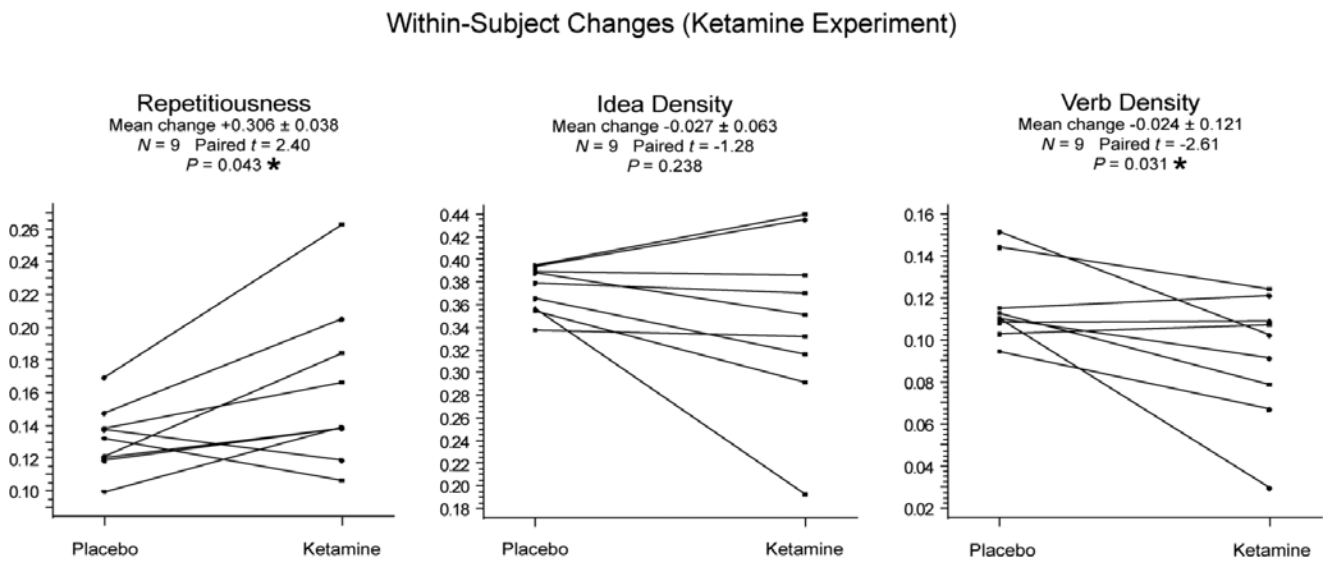

Figure 3 Ketamine experiment: within-subjects changes in measured speech characteristics.

High variance of all measures with ketamine

One generalization that is evident from Fig. 2, though not predicted by our hypotheses, is that the variance of all the measures is appreciably higher in the ketamine group than in any of the others. In two instances the difference is statistically significant: repetitiousness, ketamine versus placebo, $F = 6.01$, $p = 0.02$; idea density, ketamine versus placebo, $F = 14.07$, $p = 0.001$. In exactly those cases, the means are different but fail to be statistically significant because of the high variance of the ketamine group.

From this we conclude that the effects of ketamine are highly variable from subject to subject, and that this variability makes our hypotheses unexpectedly hard to test.

Repetitiousness (perseveration)

This is the only measurement that was statistically significant in both experiments (Figs 2 and 3). Both schizophrenia and ketamine produced significantly more repetitiousness. In this respect, ketamine reproduced a symptom of schizophrenia, although the effect was apparently larger (Fig. 2, upper right, and Fig. 3). With ketamine, the effect, even though apparently large, was significant only within subjects and not between groups because of the large variance of the ketamine group.

Adler *et al*. (1999) also found a larger increase in repetitiousness with ketamine than with schizophrenia. They obtained comparable scores on all Thought, Language, and Communication scale items except perseveration, which was appreciably higher with ketamine (mean 1.3 versus 0.6, significant *prima facie* but not after their Bonferroni correction for multiple comparisons).

Perseveration is usually interpreted as executive impairment, but repetition over a relatively short interval, such as we measured, could also reflect impaired access to the lexicon (causing the speaker to try the same thing over and over) or difficulty assembling complete linguistic structures (somewhat like stammering). Regardless of its neural basis, it is apparently a characteristic that schizophrenia and ketamine have in common.

Idea density and verb density

Idea density was not significantly reduced either in schizophrenia or with ketamine. As Fig. 2 shows, the means were slightly lower than in the control groups, but the difference was not statistically significant. The variance of idea density was much higher with ketamine than in schizophrenia or in either control group.

From this we conclude that neither schizophrenia nor ketamine produces a drop in idea density like that observed in Alzheimer's disease. Verb density, a component of idea density, was significantly reduced with ketamine but not in schizophrenia (Fig. 2, bottom; Fig. 3, right).

Reduced use of verbs is manifested as a tendency to speak in noun phrases rather than sentences. Here are two samples of the same volunteer's speech, with and without ketamine (not describing the same picture, of course):

With ketamine, showing reduced use of verbs:

It looks like a scene from a port of something. There's uh a sunset. There's a river. There's a boat. Someone on a – on a bridge type – type of thing and a house.

Without ketamine, with normal use of verbs:

It's a farmyard scene. There's a a young farmer plowing a field with his horse. And a young girl. It looks like she's going to college or something with some books. And there's another woman. Sort of farmer type woman leaning against a tree.

Recall that in each case the speaker is describing a picture, a task that can be performed either with whole sentences or with a list of noun phrases without verbs. Thus, some type of picture description is probably an ideal task for eliciting reduced versus normal use of verbs.

It is well established that verbs are harder to produce than nouns (in the sense that production is more easily impaired), both for healthy speakers in experimental situations (Szekely *et al*., 2005 and literature reviewed there) and in aphasic speakers, especially if the latter are sentence-production-impaired (Bak *et al*., 2001; Berndt *et al*., 2002; Druks, 2002). Verb production impairment has been attributed to executive impairment (Silveri *et al*., 2003), although a simpler explanation is that verbs simply require more cognitive or linguistic processing, since they normally require arguments (subject, object, etc.) whereas nouns do not.

Regardless of the neural basis of reduced use of verbs, it is an effect that distinguishes ketamine from schizophrenia. Classic studies of idea density (e.g. Snowdon *et al*., 1996) should be re-examined to determine whether reduced use of verbs was actually the phenomenon observed in those studies

Strengths and weaknesses of this study

Dosage regimen The dosages of ketamine in this experiment were in keeping with those in the literature reporting on subjective and objective effects of ketamine (Newcomer *et al*., 1999). The possibility remains that a different dose of ketamine would have produced a more accurate simulation of schizophrenia.

Magnitude of changes As percentages of baseline score, the changes that we report as significant were relatively large. Comparing schizophrenia to healthy controls, mean repetitiousness was up 20%. Comparing ketamine to placebo, the mean intra-subject increase in repetitiousness was 23% of the mean placebo score, and the mean intra-subject decrease in verb density was 20.5% of the mean placebo score.

Although these numbers have not been calibrated to establish a norm, they are large enough to lead us to believe that the changes are clinically and neuropsychologically meaningful.

Multiple comparisons We tested three hypotheses on two sets of data, resulting in a grand total of six significance tests,[2] three of which were significant.

Because the hypotheses are separate, we treat the significance tests separately (cf. Perneger, 1998). They are not multiple tests of a single null hypothesis.

Each hypothesis was indeed tested on two experiments, and arguably, two-way Bonferroni correction should be performed; it would cut the 0.05 *p*-value threshold in half. However, in all cases we performed two-tailed *t*-tests even though the hypotheses were one-sided. Switching to one-tailed *t*-tests would also cut the *p*-values in half and leave our conclusions as they are.

[2] Fig. 2, left two columns, and Fig. 3. The right two columns of Fig. 2 are shown with significance values for comparison but were not used to draw conclusions.

Although the effect sizes were small, all of the significant outcomes were in the predicted direction, and hence it does not seem likely that null hypotheses were rejected while they were in fact true. It should be kept in mind that this is a preliminary study and the results should be interpreted as directional.

Method of speech elicitation using pictures The speech samples were elicited with pictures from the TAT, whose original purpose was to elicit emotional concerns rather than simple prose descriptions. Different pictures, designed to be relatively easy to describe, would presumably be more suitable for an experiment of this type. Other special-purpose paradigms may be useful; for example, lexical access can be probed very precisely with the picture-word interference paradigm (Miozzo and Caramazza, 2003).

Two other concerns are that the two experiments (schizophrenia and ketamine) used different sets of TAT pictures and elicited speech samples of considerably different length (946 ± 262 words for schizophrenia versus 256 ± 107 words for ketamine).

Note however that our measurements were designed to be independent of text length; all involve dividing by the total number of words, and unlike for example the widely used type-token ratio, none of our measurements involve quantities that inherently change with the size of the text. Moreover, Fig. 2 makes it obvious that the control groups for both experiments received very similar scores.

Another possible issue is visual processing, which is known to be impaired in schizophrenia (Butler *et al*., 2005). Repetition in speech and reduced use of verbs could result from, respectively, disorganized processing of the image and a perceptual bias in favor of things rather than actions, rather than from a disorder of speech *per se*. This question deserves further investigation. Even so, our conclusions about whether ketamine models schizophrenia are unaffected; the only issue is what domain(s) of cognition are involved.

Sample size, sensitivity and specificity The small sample size used does not allow us to conclude much in the cases where no significant difference was found. Further, the relatively small number of observations in the between-groups comparison for schizophrenia left us with much less statistical power than the within-subjects comparison for ketamine. A larger sample of schizophrenia patients vs. controls might have shown the same results as the ketamine experiment, but that remains to be demonstrated in subsequent work.

Further investigation of specificity is warranted. We found a difference between schizophrenia and ketamine, but we do not know if the schizophrenia results also apply to other disorders, such as depression or Alzheimer's disease, nor whether the ketamine results also apply to other sedating drugs. These questions can be investigated in further experiments.

What we *can* conclude is that our methods have high sensitivity. Even with the small sample size used, in both schizophrenia and ketamine, significant differences were found between 'normal' and 'abnormal' speech, interpretable and in line with our hypotheses.