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Chapter 6

Language disturbances in schizophrenia: the relation with antipsychotic medication

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Abstract

Language disturbances are key aberrations in schizophrenia. Little is known about the influence of antipsychotic medication on these symptoms. Using computational language methods, this study evaluated the impact of high versus low dopamine D2 receptor (D2R) occupancy antipsychotics on language disturbances in 41 patients with schizophrenia, relative to 40 healthy controls. Patients with high versus low D2R occupancy antipsychotics differed by total number of words and type-token ratio, suggesting medication effects. Both patient groups differed from the healthy controls on percentage of time speaking and clauses per utterance, suggesting illness effects. Overall, more severe negative language disturbances (i.e. slower articulation rate, increased pausing and shorter utterances) were seen in the patients that used high D2R occupancy antipsychotics, while less prominent disturbances were seen in low D2R occupancy patients. Language analyses successfully predicted drug type (sensitivity=80.0%, specificity=76.5%). Several language disturbances were more related to drug type and dose, than to other psychotic symptoms, suggesting that language disturbances may be aggravated by high D2R antipsychotics. This negative impact of high D2R occupancy drugs may have clinical implications, as impaired language production predicts functional outcome and degrades quality of life.
Inroduction

Disordered language is a hallmark feature of schizophrenia. Varying degrees of aberrant language can be observed in up to 80% of patients with schizophrenia (Rodriguez-Ferrera et al., 2001), and have been shown to comprise a broad variety of abnormalities in semantics, syntax, and phonology (Çokal et al., 2018; Corcoran, Carrillo, Fernández-Slezak, et al., 2018; Elvevåg et al., 2007; Sevilla et al., 2018). Most common among these are poverty of speech (alogia), increased pausing, reduced variation in intonation (monotone speech), and disturbances in the (discursive) coherence, such as derailment and tangentiality (Covington, He, Brown, Naci, et al., 2005; DeLisi, 2001; Kuperberg, 2010). Since language is of primary importance for social relations and daily interactions (Oliveira et al., 2015), it is a worrisome observation that language is affected in this patient group, as patients with schizophrenia are known to experience difficulties in maintaining trustworthy relations with others (Oliveira et al., 2015) and are at an increased risk of social isolation (Michael & Park, 2016). Language disturbances in schizophrenia may negatively impact social relations in several ways. For example, reduced speech rate is known to negatively influence judgments of the speaker by others. Slower speakers are considered less truthful, less fluent, and less persuasive (Apple et al., 1979; De Waele et al., 2017). Disturbances in spontaneous speech can therefore have a negative impact on a broad range of life experiences (Jackson et al., 1989). Moreover, abnormalities of language in schizophrenia are predictive of functional outcome (Bowie & Harvey, 2008; Dickinson et al., 2006), have a negative impact on both objective and subjective quality of life (Tan et al., 2014), and thus greatly impact rehabilitation.

Antipsychotics are considered the first choice of treatment for schizophrenia, with positive effects reported on hallucinations, delusions and disorganization (Leucht et al., 2009, 2013; Sommer et al., 2012). However, little is known about the remedying effects of antipsychotic medication on language disturbances. Importantly, there is reason to assume that antipsychotic drugs may contribute to some of these language perturbations (Sinha et al., 2015a, 2015b). Specifically, antipsychotic drugs’ effects on dopamine receptors can be hypothesized to impair language, in several ways.

Firstly, negative language symptoms with a cognitive basis, such as poverty of speech and incoherence, are likely to be affected by antipsychotic medication, since antipsychotic drugs potentially increase these symptoms by blocking dopamine...
receptors in prefrontal brain areas that are thought to be hypodopaminergic in patients with a psychosis (Davis & Kahn, 1991; Meyer-Lindenberg et al., 2002; Okubo et al., 1997).

Secondly, binding to the striatal dopamine receptor is known to cause extrapyramidal side effects (EPS), such as tremor, bradykinesia and rigidity (Chetrit et al., 2009; Richelson, 1984). Although EPS are classically known as limb movement disturbances, they also affect the motor components of spoken language production, i.e., the programming and execution of articulatory movements (Bär et al., 2004). Indeed, drug-induced EPS, or severe Parkinsonism, is characterized by slow, hesitant and soft speech, indicating that medication affects planning and controlling of articulatory movements (Bär et al., 2004).

While all antipsychotic drugs block the dopamine D2 receptor (D2R), some do so quite extensively and others more subtly. They can be classified based on their mechanism of action. For example, clozapine and quetiapine bind more loosely to the D2R than dopamine itself (henceforth low D2R occupancy drugs; Seeman & Tallerico, 1998). By contrast, typical antipsychotics such as haloperidol and risperidone are ‘strong’ D2R antagonists (henceforth high D2R occupancy drugs), as they bind more tightly to the receptor than dopamine. It can, therefore, be expected that not all types of antipsychotic medication will have similar effects on language production. Rather, the extent to which the medication binds to dopamine receptors may play a vital role in this.

Language production involves at least three processing systems: the conceptualizer, the formulator and the articulator (Levelt, 1993). Conceptualizing involves the organizing of ideas and intentions into a preverbal message. The formulator translates this preverbal message into a linguistic structure with its corresponding meaning and form. Finally, articulation involves the programming and execution of a predetermined phonetic plan by the muscles of the articulatory tract. The processing systems involved in language production can therefore also be categorized as being either primarily cognitive (conceptualizer and formulator) or motoric (articulator) in nature. Language production is thus a shared motoric and cognitive process, and is therefore likely to be affected by dopamine blockage in both striatal as well as prefrontal brain areas.

Previous studies assessing language and speech in schizophrenia revealed that at the level of speech delivery, proportion of spoken time and speech rate are decreased, and (clause initial) pauses are increased (Cohen et al., 2014; Çokal et
al., 2019; Parola et al., 2020). As regards language structure and content, research indicates that syntactic complexity is decreased (Covington, He, Brown, Naçi, et al., 2005), which is reflected in short sentences with reduced embedding and limited lexical diversity. Furthermore, schizophrenia patients suffer from word-finding issues (mostly related to content words such as nouns or verbs), resulting in longer pauses and disfluencies (Covington, He, Brown, Naçi, et al., 2005).

Summarizing, language disturbances are a core symptom of schizophrenia, which greatly impacts social and functional outcomes and quality of life. Little is known about the impact of antipsychotic medication on language in patients with schizophrenia. As EPS can negatively affect the articulatory system (i.e., programming and execution of articulatory movements), and brain areas implicated in the cognitive components of language production (conceptualizing and formulating) are known to be negatively affected by antipsychotic drugs that block dopamine receptors, such drugs may have a relatively negative impact on spoken language in schizophrenia patients. From the above follows the hypothesis that language will be more severely disturbed (e.g. increased pauses and slower speech rate) in patients with schizophrenia that use high D2R occupancy medication than in those using low D2R occupancy medication. In the present study, we set out to test this hypothesis by comparing spoken language samples of schizophrenia patients on language variables that are known to be disturbed in schizophrenia (Cohen et al., 2014; Covington et al., 2005; de Boer et al., 2020; Parola et al., 2020 - see Table 1 for an overview). Patients were divided into two categories based on dopamine binding profiles, namely patients with low D2R occupancy drugs (i.e. quetiapine, paliperidone, olanzapine and clozapine) or high D2R occupancy drugs (i.e. aripiprazole, risperidone, flupentixol, amisulpride and haloperidol). We additionally analyzed language produced by a healthy control group for comparison and explored the relation with psychotic symptom severity.
### Table 1 Description of language variables

| Variable               | Definition / calculation                                                                 | Measures                                                                 |
|------------------------|------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| articulation rate      | syllables / phonation time (Motor) speed in speech production.                           |                                                                           |
| average pause duration | total time the participant was pausing in seconds / number of pauses                     | Pauses often reflect formulating or planning language and might therefore reflect processing speed. |
| average turn duration  | average duration of a speaking turn in seconds.                                          | Average length of an answer, before another question is necessary.        |
| percentage of time speaking | time participant speaking / time interviewer speaking*100                              | Might reflect spontaneity in speech or willingness to speak.              |
| mean length of utterance (MLU) | mean length of utterance in morphemes                                                      | Sentence complexity. Greater length indicates more complex sentences.     |
| type-token ratio (TTR) | # types / # tokens                                                                       | Lexical diversity. Types: the number of different words used in the sample. Tokens: all words in the sample. This number goes from .001 to 1.0. Low values indicate a lot of repetition, high values means each word in the sample was different. High TTR indicates fewer syntactical structures. |
| clauses per utterance | Average number of clauses per utterances.                                                 | Grammatical complexity. More clauses per utterance indicate more syntactical complex sentences. |
| noun verb ratio        | # nouns / # verbs                                                                         | Number of nouns per verbs. Might reflect specific difficulty with either nouns or verbs. |
| open closed ratio      | # open class words / # closed class words                                                  | Content words versus function words. Open class: content words. Word class accepts new members easily. Closed class: function words. Word class does not easily accept new members. Might reflect specific difficulty with either content or function words. |
| disfluencies           | # of disfluencies / # all words                                                            | Difficulties formulating sentences. All forms of disfluencies, including filled pauses and retracing as a percentage of all words. |
| pause to word ratio    | # pauses / # all words                                                                     | Indication of processing speed. Measures how many pauses are needed to formulate one word. |
Figure 1 Illustration of the interview and language measures

Figure legend: The speech waves (oscillograms) are for illustrative purposes only and do not reflect the actual recordings of these sentences.
RESULTS

Demographics

Clinical and demographic data are shown in Table 2. The groups did not differ with regard to sex and age. Patients had received less education than healthy controls, and there was no difference in parental education level between groups. Symptom severity as measured by the Positive And Negative Syndrome Scale (PANSS) as well as drug dose as measured in chlorpromazine equivalent dose did not differ between patients with high or low D2R occupancy medication.

Language variables between the groups

For an overview of the language variables, see Figure 1 and Table 1. Schizophrenia patients with high versus low D2R occupancy medication and healthy controls were compared on language variables using a MANCOVA.

To correct for the influence of age, sex and education level on normal variation in language, these variables were entered as covariates in the model. The MANCOVA revealed a main effect of group status on language (Pillai's trace = .526, F (2, 80) = 1.843, \(p = .016\), partial \(\eta^2 = .263\)). Furthermore, a main negative effect was found for age (Pillai's trace = .328, F (1, 80) = 2.477, \(p = .010\), partial \(\eta^2 = .328\)) and male sex (Pillai's trace = .395, F (1, 80) = 3.315, \(p = .001\), partial \(\eta^2 = .395\)), but not for education level. No interaction effects were found between the independent variables. Post-hoc tests revealed that patients that use high D2R occupancy drugs differ from low D2R occupancy patients on a number of language variables, including total number of words and Type-Token Ratio (TTR, i.e. a measure for lexical diversity), as well as from healthy controls on several language variables, including articulation rate, TTR, Mean Length of Utterance (MLU). However, low D2R occupancy patients do not differ from healthy controls on most aspects of language (see Table 3).
Table 2 Demographic characteristics of patients with schizophrenia with high 2DR occupancy medication, low D2R occupancy medication and healthy controls

|                          | High D2R | Low D2R | HC  | Test statistic | p-value |
|--------------------------|----------|---------|-----|---------------|---------|
| n                        | 23       | 18      | 40  |               |         |
| Sex, male : female, n    | 17 : 6   | 14 : 4  | 36 : 4 | χ² = 3.038    | .219    |
| Age, mean (SD)           | 28.5 (9.04) | 28.3 (9.39) | 31.7 (11.71) | F(2,78)=1.002 | .372    |
| Years of education, mean (SD) | 13.2 (2.63) | 12.2 (2.94) | 14.8 (2.20) | F(2,77)=7.446 | .001    |
| Parental years of education, mean (SD) | 12.7 (2.93) | 12.3 (2.85) | 12.8 (3.10) | F(2,68)=.128 | .880    |
| Self-reported language fluency, n |         |         |     |               |         |
| Fluent in Dutch only     | 13       | 15      | 19  | χ² = 7.357    | .118    |
| Fluent in two languages  | 9        | 3       | 17  |               |         |
| Fluent in three language | 1        | 0       | 4   |               |         |
| Duration of illness years, mean (SD) | 4.5 (5.55) | 5.1 (7.49) |     | MW=189        | .871    |
| Total PANSS, mean (SD)   | 52.0 (11.98) | 52.1 (8.57) |     | F(1,39)=.002  | .963    |
| PANSS positive           | 10.7 (4.72) | 11.2 (2.98) |     | F(1,39)=.136  | .714    |
| PANSS negative           | 14.0 (5.12) | 14.9 (4.96) |     | F(1,39)=.313  | .579    |
| PANSS general            | 27.3 (6.51) | 26.1 (4.95) |     | F(1,39)=.424  | .519    |
| Psychotic disorder, n    |          |         |     | χ²=4.244     | .236    |
| Schizophrenia            | 8        | 5       |     |               |         |
| Schizoaffective disorder | 4        | 3       |     |               |         |
| Schizophreniform disorder| 0        | 3       |     |               |         |
| Psychosis NOS            | 12       | 7       |     |               |         |
| Chlorpromazine equivalent (mg), mean (SD) | 347.8 (217.87) | 518.6 (302.9) |     | MW=107.5      | .056    |
| Antipsychotic medication, n |       |         |     |               |         |
| Amisulpride              | 2        |         |     |               |         |
| Aripiprazole             | 15       |         |     |               |         |
| Flupentixol              | 1        |         |     |               |         |
| Haloperidol              | 3        |         |     |               |         |
| Risperidone              | 2        |         |     |               |         |
| Clozapine                | 5        |         |     |               |         |
| Olanzapine               | 5        |         |     |               |         |
| Paliperidone             | 4        |         |     |               |         |
| Quetiapine               | 4        |         |     |               |         |

Table legend: SD: standard deviation, n: sample size, High D2R: schizophrenia patients with high dopamine D2 receptor occupancy medication, low D2R: schizophrenia patients with low dopamine D2 receptor occupancy medication, HC: healthy controls, PANSS: positive and negative syndrome scale, NOS: not otherwise specified, MW: Mann-Whitney U.
Relation with antipsychotic medication

A binary logistic regression model was used to investigate whether language variables could predict whether patients used a high or low D2R occupancy drug. Drug dosage was entered as a covariate. The optimal model had high predictive power (Nagelkerke approximation of $R^2 = .560$), and the Hosmer-Lemeshow test for goodness-of-fit was non-significant ($p = .932$). The following language variables were included in the final model: mean pause duration, MLU, TTR and speaking turn duration. Patients with high and low D2R occupancy could be classified with this model with a sensitivity of 80.0% and a specificity of 76.5%.

Relation with antipsychotic medication and psychotic symptoms

To assess the effects of medication type and dose as well as psychotic symptoms, multivariate linear regression analyses were performed for each of the language variables. Psychotic symptoms, drug type (high or low D2R drugs) and drug dosage were entered as predictors. Unstandardized (B) and standardized ($\beta$) regression coefficients for each predictor in the separate models as well as the predictive utility of the entire model are reported in Table 4. The models for noun verb ratio and percentage of disfluencies were not significant. The variance in pause duration and the number of clauses per utterance were predicted solely by aspects of medication use (D2R occupancy for both, and dosage for pause duration). Speaking turn duration was only predicted by PANSS positive. Articulation rate, percentage of time speaking, MLU, TTR and pause to word ratio were found to be affected by both symptoms and D2R occupancy.
Table 3 Language characteristics of patients with schizophrenia with high 2DR occupancy medication, low D2R occupancy medication and healthy controls

| Language variables               | (A) High D2R $n = 23$ Mean ± SE | (B) Low D2R $n = 18$ Mean ± SE | (C) HC $n = 40$ Mean ± SE | F-statistic | p-value | Post-hoc analyses † |
|---------------------------------|-------------------------------|-------------------------------|--------------------------|-------------|---------|---------------------|
| Total number of words           | 1043.0 ± 113.60               | 1485.6 ± 140.56               | 1768.9 ± 101.18          | 11.544      | <.0001**| .025* - <.0001**    |
| Articulation rate               | 5.5 ± .20                     | 5.9 ± .25                     | 6.2 ± .18                | 3.156       | .049*   | -                   |
| Pause duration (sec)            | 1.03 ± .043                   | .90 ± .053                    | .86 ± .038               | 2.850       | .064    | -                   |
| Speaking turn duration          | 8.7 ± 1.54                    | 7.2 ± 1.90                    | 10.8 ± 1.37              | .684        | .508    | -                   |
| Percentage of time speaking     | 69.2 ± 1.98                   | 70.0 ± 2.45                   | 77.3 ± 1.76              | 4.999       | .009**  | -                   |
| MLU                             | 13.4 ± 1.37                   | 16.8 ± 1.69                   | 19.1 ± 1.22              | 6.539       | .002**  | -                   |
| TTR                             | .20 ± .008                    | .17 ± .009                    | .16 ± .007               | 7.038       | .002**  | .019* - <.0001**    |
| Clauses per utterance           | .568 ± .005                   | .572 ± .006                   | .588 ± .004              | .783        | .461    | -                   |
| Noun verb ratio                 | .72 ± .017                    | .69 ± .021                    | .68 ± .015               | .649        | .526    | -                   |
| Open closed ratio               | .85 ± .014                    | .82 ± .017                    | .82 ± .012               | .424        | .656    | -                   |
| Percentage of disfluencies      | 6.3 ± .52                     | 6.2 ± .65                     | 5.2 ± .47                | 1.496       | .231    | -                   |
| Pause to word ratio             | 13.4 ± .77                    | 11.3 ± .95                    | 9.9 ± .68                | 4.033       | .022*   | -                   |

Table legend: Table displays estimates of means, covariates included in the model: age, sex and years of education. High D2R: schizophrenia patients with high dopamine D_2 receptor medication, low D2R: schizophrenia patients with low dopamine D_2 receptor medication, HC: healthy controls, SE: standard error, vs: versus, *significant at the level of $\alpha = .05$** significant at the level of $\alpha = .01$, p-values are Bonferroni corrected, MLU: mean length of utterance, TTR: type-token ratio. For explanation of the language variables, see Table 1.† only significant p-values are reported.
Table 4 Regression analyses of predictors of language disturbances in schizophrenia patients

| Language variables | Significant predictor(s) | B  | Confidence Interval B (95%) | β     | Adjusted R² | p-value (uncorr.) | p-value (FDR corr.) |
|-------------------|--------------------------|----|-----------------------------|-------|-------------|------------------|-------------------|
| 1. Articulation rate | PANSS positive | .067 | .003 - .132 | .299 | .298 | .002** | .004** |
|                   | PANSS negative | -.069 | -.120 - -.017 | -.380 | -.380 | .049* | .055 |
|                   | D2R occupancy | -.359 | -.659 - -.059 | -.342 | -.342 | .114 | .049* |
| 2. Pause duration  | D2R occupancy | .089 | .010 - .167 | .380 | .380 | .049* | .055 |
|                   | Dosage (mg/l) | .0002 | -.00002 - .0005 | .304 | .304 | .304 | .304 |
| 3. Speaking turn duration | PANSS positive | .917 | .386 - 1.447 | .510 | .510 | .001** | .002** |
| 4. Percentage of time speaking | PANSS negative | -1.178 | -1.664 - -.692 | -.574 | -.574 | <.0001** | <.0001** |
|                   | PANSS general | .626 | .210 - 1.043 | .356 | .356 | .356 | .356 |
|                   | D2R occupancy | -6.525 | -9.302 - -3.748 | -.547 | -.547 | .114 | .049* |
| 5. MLU             | PANSS negative | -.498 | -.911 - -.085 | -.348 | -.348 | .001** | .003** |
|                   | D2R occupancy | -3.988 | -6.384 - -1.593 | -.480 | -.480 | .001** | .003** |
| 6. TTR             | PANSS negative | .003 | .0005 - .005 | .333 | .333 | <.0001** | <.0001** |
|                   | PANSS general | -.003 | -.004 - -.001 | -.412 | -.412 | .001** | .003** |
|                   | D2R occupancy | .025 | .013 - .037 | .558 | .558 | .001** | .003** |
| 7. Clauses per utterance | D2R occupancy | -.008 | -.017 - -.00001 | -.325 | -.325 | .050 | .050 |
| 8. Open closed ratio | PANSS negative | .006 | .002 - .009 | .442 | .442 | .006** | .009** |
|                   | D2R occupancy | .022 | -.001 - .044 | .294 | .294 | .006** | .009** |
| 9. Pause to word ratio | PANSS negative | .261 | .042 - .481 | .360 | .360 | .008** | .010** |
|                   | D2R occupancy | 1.598 | 2.875 - 3.800 | 2.875 | 2.875 | .008** | .010** |

Legend: The table displays unstandardized (B) and standardized (β) regression coefficient for each significant predictor, in a model for each of the language variables. The adjusted R² and ANOVA p-values display the fit and significance of the full model. Predictors entered into the model were: PANSS positive, negative and general, D2R occupancy and chlorpromazine equivalent dose. PANSS: Positive And Negative Syndrome Scale, D2R: dopamine D2 receptor, FDR: false discovery rate, uncorr.: uncorrected, corr.: corrected *: indicates significance at the level of α=.05, **: indicates significance at the level of α=.01, MLU: mean length of utterance, TTR: type-token ratio. No significant relations were found between PANSS and medication and noun verb ratio and percentage of disfluencies. *Chlorpromazine equivalent dose.
DISCUSSION

Using computational language and speech analysis tools, this study evaluated the impact of antipsychotic medication type (high versus low D2R occupancy) on language disturbances in schizophrenia. We showed that patients who use high D2R occupancy drugs, such as aripiprazole, haloperidol and risperidone, differ from patients who use low D2R occupancy drugs on total number of words and TTR, suggesting an effect of medication. Both patient groups differ from healthy controls on percentage of time speaking and clauses per utterance, suggesting illness effects. Overall, patients who use high D2R occupancy drugs have more severe negative language disturbances (i.e. slower articulation rate, increased and prolonged pauses and shorter utterances with fewer clauses), while less prominent disturbances are seen in patients who use low D2R occupancy drugs, such as clozapine and olanzapine. Language analyses were successful in predicting whether the recorded discourse belonged to a patient using high versus low D2R drugs. Finally, various language disturbances (MLU, TTR, pause to word ratio and clauses per utterance) were related to the use of high D2R occupancy drugs and the dosage of those drugs, rather than to the severity of the psychotic symptoms, which again suggests medication effects over illness effects.

As hypothesized, our results demonstrate that the use of high D2R occupancy drugs is associated with more severe language disturbances in schizophrenia compared to low D2R occupancy drugs, as reflected by reduced language production (i.e. total number of words produced) compared to low D2R occupancy drugs. Clinically, this might be described as alogia or poverty of speech, which is considered a negative symptom. This is most likely related to an increased hypodopaminergic state in the prefrontal cortex, as medication-induced decrease of dopamine in the prefrontal cortex impairs cognitive functioning in general and induces negative symptoms (Abi-Dargham et al., 2002; Braver et al., 1999).

Our results further demonstrated that patients who use high D2R occupancy drugs differ from healthy controls on several language parameters (pause duration, MLU, clauses per utterance, pause to word ratio), while low D2R occupancy patients do not or to a lesser degree. We interpret these results as indicative of two individual mechanisms of action. On the one hand, the finding that high D2R occupancy drugs are associated with increased pause rate, pause duration and reduced clauses per utterance, may be related to disturbances in language processing. Information transfer between prefrontal and temporal
language-relevant regions is crucial for efficient language production (Friederici, 2015; Friederici & Gierhan, 2013). A recent study by our group revealed that integrity of white-matter language pathways is associated with broad language disturbances in schizophrenia (de Boer, van Hoogdalem, et al., 2020). High D2R occupancy drugs may induce a hypodopaminergic stage and reduce information processing in language tracts, and thus give rise to language disturbances related to cognitive fluency or efficiency (i.e. pauses) and cognitive effort or complexity (i.e. MLU, clauses per utterance, TTR). Indeed, previous research in schizophrenia has shown that hypodopaminergic states are associated with white-matter integrity in the frontal cortex (Walther et al., 2012). Moreover, dopamine replacement therapy in Parkinson's disease is associated with both increased connectivity in white-matter language pathways improved and speech production (Elfmarková et al., 2016). On the other hand, patients using high D2R occupancy drugs spoke more slowly than controls (i.e. articulation rate), which can be related to blockage of the extrapyramidal system which has a slowing effect on articulation. In like manner, patients with Parkinson's disease show a characteristic pattern of declining speech and articulation rate with illness progression (Logemann et al., 1978; Martínez-Sánchez et al., 2016; Sapir et al., 2008).

Our finding that high D2R occupancy drugs (such as risperidone) are associated with increased pausing, provides evidence that increased pausing is not related to sedative effects of antipsychotic drugs. Many of the low D2R occupancy drugs are highly sedating (e.g. olanzapine, quetiapine and clozapine), which is known to negatively influence cognitive performance (Hill et al., 2010); instead we found increased pausing to be associated with less sedative antipsychotics.

A key question is whether the relative increase in language disturbances is caused by the use of high D2R occupancy drugs and should thus be regarded an adverse effect, or whether language disturbances in schizophrenia are relatively more severe in the high D2R occupancy group because they are better suppressed by low D2R occupancy drugs. The design of the current study does not allow for a discrimination between these mechanisms of action. Language disturbances are present in children who later develop psychosis (Gooding et al., 2013) and in youths at clinical high risk for psychosis (Bedi et al., 2015b; Corcoran, Carrillo, Fernández-Slezak, et al., 2018; Gupta et al., 2018), in the absence of antipsychotic exposure, and are associated to the severity of psychotic symptoms in this group (Sichlinger et al., 2019). Moreover, language disturbances are also present in patients with
bipolar disorder that do not use antipsychotic medication (Andreasen, 1979; Mota et al., 2014; Yalincetin et al., 2017). Within the small existing literature base dedicated to this topic, there is some evidence that language disturbances respond well to antipsychotic medication (haloperidol; Gold & Hurt, 1990). Indeed, some have suggested that antipsychotic medication improves communication since it is associated with reduced incoherence and tangentiality (Clark et al., 1994). However, there is also some evidence that antipsychotics reduce intelligibility of speech and induce poverty of speech (Sinha et al., 2015a, 2015b). Antipsychotics can also cause acute laryngeal dystonia or laryngeal dyskinesia, causing stridor and thereby negatively impacting speech (Ganesh et al., 2015; Rowley et al., 2001). Furthermore, in Huntington’s disease, research shows that antipsychotic medication decreases speech rate and induces excessive loudness and pitch deviations (Rusz et al., 2014). In contrast, dopamine replacement therapy in Parkinson's disease has positive effects on speech tempo and prosody (Rusz et al., 2016). It is important to bear in mind that the field is in its early stages and our results are preliminary, and corresponding interpretations should, therefore, be regarded with caution. Moreover, not all language disturbances are the same; alogia, flat intonation (both negative symptoms), highly associated or incoherent language (both positive symptoms) might all be considered aberrant language production, however the mental processes underlying these aberrations clearly differ. Therefore, the effects of antipsychotic medication on these language aberrations may differ as well. Replication in a larger sample is needed to fully understand the complex relation between language and antipsychotic medication.

The main limitations of this study include the absence of medication naïve or medication-free patients as well as a nonpsychotic patient group with antipsychotics, which precluded a pure assessment of the influence of antipsychotic medication on language production. Further, because a cross-sectional design was used, medication usage was not randomized and the language disturbances we observed could not be followed over time. Moreover, we could not rule out a bias in prescribing patterns of high and low D2R occupancy drugs, although clinical guidelines do not express any preference between antipsychotic drugs (except for clozapine). For this reason, a causal relation with the use of medication could not be established. Due to the design, we were unable to meaningfully examine the impact of neuropsychological deficits or other confounding variables (e.g., premorbid functioning, rapport, as well as illness-related factors such as sleep dysfunction,
depression and paranoia) on language production. This remains an important topic for future research. It should be noted that we found an increased TTR in the patients as compared to the healthy controls. This is most likely an effect of sample size (total number of words produced), since the patients produced less words in total and TTR is known to be higher for smaller speech samples (Hess et al., 1986). Furthermore, it is important to note that a large part of our high D2R occupancy patients used aripiprazole (65%). As stated above, aripiprazole is categorized as a strong D2R antagonist, although it also has some agonistic effects (Shapiro et al., 2003). A related issue is that clozapine was grouped into the low D2R occupancy group, while clozapine is in general reserved for treatment of refractory patients with schizophrenia. Thus, replication in a large independent sample will be an important future research direction, in order to have sufficient statistical power to address the effects of each of the drugs individually. Of note, in the current study we only evaluated the effects of dopaminergic receptor occupancy while most antipsychotic drugs also act on other neurotransmitter systems (e.g. serotonergic and anticholinergic receptors). For example, anticholinergic medication has been shown to negatively impact spoken language by inducing dryness of the oral and nasal mucosa (Nemr et al., 2018). Further research is needed to unravel the effects of these neurotransmitters on language disturbances. It should be noted that although no significant differences in language fluency were found between the groups, bilingualism is an important confounder in language research in schizophrenia. Ethnic minority groups in Western countries have an increased risk of developing schizophrenia, and more specifically linguistic distance to the majority language has been associated with increased psychosis risk (Jongsma et al., 2020). Given the small sample size, this factor could not be fully explored in the current study, therefore further research is needed to assess the influence of bilingualism on language in schizophrenia.

We recognize and appreciate that there are several other approaches to quantify language disturbance in schizophrenia (de Boer, Brederoo, et al., 2020). In the last decade, natural language processing analyses, specifically semantic space analyses and phonetic or prosodic methods, have been applied to language production in schizophrenia (Bedi et al., 2015a; Corcoran, Carrillo, Fern, et al., 2018; de Boer et al., 2018; Rezaei et al., 2019; Tahir et al., 2019). These are important developments that merit a future study designed to address the potential effects of medication on these specific analyses.
Our findings have several implications. First, as language is a highly important source of information in the psychiatric evaluative process, clinicians should be aware that poverty of speech in patients might be at least partly an effect of (highly dopaminergic) medication. Deteriorated language may, therefore, not necessarily be a sign of active psychosis. Second, since many schizophrenia patients require sustained pharmacological treatment to prevent relapses, research on language disturbances has been performed mostly in participants that are on antipsychotic medication. Further studies should acknowledge that the use of antipsychotic medication can influence their analyses.

In conclusion, we demonstrate that schizophrenia patients that use high D2R occupancy drugs (e.g. aripiprazole) have more severe language disturbances compared to patients that use low D2R occupancy drugs (e.g. olanzapine, quetiapine) and healthy controls, irrespective of the severity of their psychotic symptoms. Our results indicate that language disturbances are better treated by low D2R occupancy drugs, or that some language disturbances might (in part) be caused by dopaminergic effects of high D2R occupancy drugs. Language disturbances are common and greatly impact social and functional outcome and quality of life in schizophrenia. Further research is needed to evaluate possible iatrogenic effects of medication on spoken language.

**METHODS**

**Participants**

A total of 81 participants, 41 patients with a schizophrenia spectrum disorder and 40 healthy controls were included at the University Medical Center Utrecht. Healthy controls were screened for previous or current mental illness using the Comprehensive Assessment of Symptoms and History (CASH; Andreasen et al., 1992) by a neuropsychologist. Patients were diagnosed by their treating psychiatrist; the diagnosis was confirmed using the outcome of the CASH or the Mini International Neuropsychiatric Interview 5.0.0. (M.I.N.I. Plus; Sheehan et al., 1998) by the first author or a neuropsychologist and a second rater for consensus diagnosis. Participants were included if they were 1) age eighteen or above and 2) a native speaker of Dutch. Bilingual participants were included if Dutch was (one of) their main language(s). An additional inclusion criterion for patients was the presence of a DSM-IV diagnosis of: 295.x (schizophrenia, schizophreniform
disorder, schizoaffective disorder) or 298.9 (psychotic disorder NOS). General exclusion criteria were the presence of uncorrected hearing disabilities or speech impediments (such as stutter). Healthy controls were excluded in case of any current or previous mental illness, or a family history of psychotic symptoms. The severity of psychotic symptoms was assessed in all patients with the PANSS (Kay et al., 1987). This study was reviewed and admitted by the Ethical Review Board of the University Medical Center Utrecht. Written informed consent was obtained from all participants. Participants received a small monetary award (ten euros).

**Language data acquisition and processing**

To elicit spontaneous speech we (J.B., A.V. and trained research assistants) conducted semi-structured interviews varying from five to thirty minutes in length (average fourteen minutes). Participants were informed that the research involved the analysis of ‘general experiences’; only after completion of the interview were they told that the research also focuses on the way they speak. The interviews took place between December 2015 and March 2018.

A set of questions was used in the interview to control for potential variations in language due to the topic that was discussed. All questions concerned ‘neutral’ general life experiences; topics that could be expected to have markedly different emotional valence for patients and healthy controls were not addressed. For instance, topics such as ‘quality of life’ or ‘health’ were avoided. If for any reason a subject did not want to answer a question, the interviewer would move on to the next question. For a list of the questions, see supplementary Table 1.

An AKG-C544l head-worn cardioid microphone was used to record the subject’s speech. The first 39 interviews were conducted using a single AKG-C544l head-worn cardioid microphone, worn by the subject, recording both the interviewer’s and the subject's speech onto a single channel. A second AKG-C544l head-worn cardioid microphone was used for the last interviews, resulting in a separate track for the subject and the interviewer. Speech was digitally recorded onto a Tascam DR40 solid state recording device at a sampling rating of 44,100 kHz with 16-bit quantization.

The digitized recordings were analyzed using the Praat software, which is standardly used for acoustic analyses of speech (Boersma & Weenink, 2013). Speakers’ speech signals were separated by hand onto two different tiers by J.B.
and A.V. (i.e. two audio tracks were created, one for the participant and one for the interviewer). Each segment of speech was coded as belonging either to the participant or the interviewer. When both speakers spoke at the same time, that speech segment was coded as belonging to both speakers. The pause that arises with switching between speakers was attributed to the speaker following the pause. All speech segments of individual participants were recombined into new audio files, which each thus contained only the recording(s) of an individual participant's speech, including pauses and other interruptions. Data files were blinded for diagnosis to prevent bias in separating the speaker. Inter-rater reliability for tier separation was assessed by having both raters perform tier separation for two of the files. Linguistic variables were then calculated for both audio files individually, after which intraclass-correlation-coefficients were calculated to assess the similarity in outcome measures for the different raters (which was 97.7 percent). All files were set to an average sound pressure level of 60dB to avoid differences in the analyses based on speaking volume.

The ‘Praat Script Syllable Nuclei v2’ was used to automatically obtain speech and articulation rates (Quené et al., 2011). The output of this script includes the following raw numbers: total number of syllables and total number of pauses. Pauses were defined as silences longer than 200ms, since shorter silences in speech can still be related to the articulation of sounds such as plosives (e.g. the /p/, which introduces a short silence in the sound wave; Rosen, 1992). The raw measures were calculated as a percentage of the duration of the participants' audio track, since they are strongly dependent on the length of the interview. The participants' audio file was transcribed using CLAN software according to the CHILDES manual (MacWhinney, 2000). In CLAN, the EVAL and FLUCALC functions were used to extract a collection of measures that reflect a person's linguistic fluency and complexity, such as total number of words used, type-token ratio (TTR), open closed ratio (i.e., a ratio of content words versus function words) as well as pausing and disfluencies (see Figure 1 and Table 1; Brundage & Bernstein Ratner, 2018).

**Classification of antipsychotic medication**

Patients were asked to bring a current list of the medication they used. The antipsychotic drugs were classified into different categories based on their
mechanism of action. Drugs such as clozapine and quetiapine bind more loosely
to the D2R than dopamine itself (Seeman & Tallerico, 1998). By contrast, typical
antipsychotics such as haloperidol and risperidone are strong D2R antagonists
since they bind more tightly to the receptor, which leads to higher receptor
occupancy by the drug. Aripiprazole is also categorized as a strong D2R antagonist,
although it also has some agonistic effects based on the cell type (Shapiro et
al., 2003). Patients were divided into two categories based on these different
dopamine binding profiles, namely patients with 1) low D2R occupancy drugs (i.e.
quetiapine, paliperidone, olanzapine and clozapine) or 2) high D2R occupancy
drugs (i.e. aripiprazole, risperidone, flupentixol, amisulpride and haloperidol;
Amato et al., 2018; Gerlach et al., 2003; Kapur & Seeman, 2001) Antipsychotic drug
dosages were recalculated into chlorpromazine equivalents to evaluate the effect
of dosage between the drugs (Leucht et al., 2014).

Data analysis
All analyses were performed in IBM SPSS Statistics version 25.0 for Windows.
Participant characteristics were compared between groups using an analysis
of variance (ANOVA) for continuous values, and a $\chi^2$ test for categorical values.
To assess both the effect of antipsychotic medication and symptom severity,
the following analyses were performed. 1) Between group (high D2R, low D2R
and healthy controls) analysis of language features was obtained through a
multivariate analysis of covariance (MANCOVA) by applying a general linear model
(GLM). The MANCOVA assumptions of linearity, normality and homoscedasticity
were checked visually by means of Q-Q plots and scatterplots of the residuals.
P-values were Bonferroni corrected to control for Type 1 errors. 2) To investigate
which language variables were associated with group membership (patients with
low versus high D2R drugs), a backward binary logistic regression was performed.
Predictors were the language variables, as well as age, gender and education level.
3) To model the effect of PANSS scores and the different types of antipsychotics
(low versus high D2R drugs) and dosage on the measures of language, MRAs were
performed. To account for possible biases due to multiple comparisons, false
discovery rate (FDR) was employed (Benjamini & Hochberg, 1995).
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**Supplementary materials**

For supplementary table 1 containing questions asked during the interview, the reader is referred to supplemental table S1 in chapter 3 of this dissertation.
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