Verbal communication disorders in schizophrenia: symptom or side-effect?

Janna de Boer

3396525

Supervisors:

Prof. dr. I.E. Sommer

Prof. dr. F.N.K. Wijnen

Research master Linguistics

Utrecht Institute of Linguistics OTS

Utrecht University

The Netherlands

Abstract

Verbal communication disturbances are a key diagnostic feature of schizophrenia. However, research on this topic is often confounded by the effects of antipsychotic medication. It therefore remains unclear which aspects of language production are influenced by antipsychotics, and which disturbances can be viewed as true psychotic symptoms. The spoken language of 42 healthy controls and 59 patients with a schizophrenia spectrum disorder was recorded and analyzed for measures of speed and quantity. For each type of antipsychotic medication, dopamine receptor blockage was estimated. Symptom severity was assessed by means of the Positive and Negative Syndrome Scale (PANSS). Overall, the psychosis patients spoke slower and produced fewer words than the healthy controls. Language measures revealed medium to strong correlations with PANSS negative and general scores. Articulation rate was negatively associated with the use of antipsychotic medication ($F(1,48) = 4.501$, $p = .039$, partial $\eta^2 = .086$). The use of antipsychotics with strong D2 receptor affinity was found to be a strong predictor of articulation rate (adjusted $R^2 = .263$), while less specific D2 antipsychotics did not show verbal side effects. Our results indicate a clear distinction between speech disturbances caused by (D2 specific) antipsychotics, and language disturbances associated with psychotic symptoms. In some cases, these negative side effects of strong D2 antagonists may be a reason to switch medication, as slow speech can be a social impediment. Furthermore, it is important to gain better insight into the effect of antipsychotics on speech, in order to adequately evaluate verbal communication disturbances as a psychotic symptom.

Key words: dopamine antagonist, language, speech, schizophrenia

Contents

1. Introduction

Schizophrenia spectrum disorders include a complex variety of psychiatric illnesses that affect approximately 2-3% of the population (Petty et al., 1995; Tordesillas-Gutierrez et al., 2015). One of the key diagnostic features of schizophrenia spectrum disorders is impaired verbal communication. In acute situations, when anamnesis is hampered because a (trustful) working-relationship between patient and psychiatrist is not yet established, verbal communication abnormalities, such as derailment, may be the only overt sign of psychosis.

Psychopathologists originally assumed that these verbal communication deficits reflected disorders of thinking (Bleuler, 1911), and hence coined the term 'formal thought disorder' (FTD); a term that refers to a variety of phenomena that result in impaired verbal communication. Researchers later argued that these verbal communication disorders should rather be described as a 'speech disorder'(Chaika, 1982; DeLisi, 2001). Indeed, the current diagnostic criteria recognize that these disturbances are a reflection of perturbed language functions, since they are now described as 'disorganized speech'(American Psychiatric Association, 2013).

Two important, and notably distinct, concepts in this line of research are 'language' and 'speech'. Language is the term used for the mental system underlying verbal behavior, which includes meaning, grammar and form. Speech is the term used for the spoken output or the *medium* of the language, the way it is produced by the vocal tract. Language can of course also be produced in writing or in gestures (sign language), which still requires similar cognitive processes to formulate sentences, without the use of the vocal tract (i.e. without articulation).

Though we have seen that communication difficulties in schizophrenia are currently described as 'disorganized speech', they are certainly not restricted to the articulatory system. Patients with schizophrenia spectrum disorders display a wide variety of language disorders including broad disturbances in semantics, pragmatics and grammatical structures (Covington et al., 2005; Kuperberg, 2010). 'Disorganized speech' would therefore better be described as 'disorganized language', which includes, but is not limited to, speech.

Language production is a complex process, which involves several different stages. According to Levelt's famous model, language production involves three separate processing systems: the conceptualizer, the formulator and the articulator (Levelt, 1993). Conceptualizing is a process that involves the organizing of ideas and intentions into a preverbal message. The message generated is the input for the second processing component; the formulator. The formulator translates this preverbal message into a linguistic structure with its corresponding meaning and form. Finally, articulation involves the 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 motor (articulator) in nature.

Despite more than a century of research on schizophrenia spectrum disorders, their exact etiology and pathology remains unclear. Consequently, little is known about the etiology of the disorganized language seen in these disorders. Nonetheless, a large body of evidence suggests that disturbances in several neurotransmitter systems are involved in the occurrence of psychotic symptoms in general. Following the dopamine hypothesis (Carlsson, 1988; Howes & Kapur, 2009; Jentsch & Roth, 1999; Meltzer & Stahl, 1976), antipsychotic drugs are meant to target this aberrant system by blocking dopamine receptors.

Since many schizophrenia patients require sustained pharmaceutical treatment to prevent relapses, research has been performed mostly in participants that are on antipsychotic medication. A recurrent field of tension in this line of research therefore is the difficulty to discriminate the effects of antipsychotic drugs from the psychotic disorder or symptomatology proper. This also holds for verbal communication disorders.

Dopamine antagonists (as employed in antipsychotics) are known to have severe extrapyramidal side effects; these motor symptoms are thought to be a direct consequence of blocking dopamine D2 receptors in the basal ganglia network (Chetrit et al., 2009; Richelson, 1984). Noting that spoken language production is a partly motoric process gives rise to the prediction that antipsychotic drugs may affect the planning and control over the articulatory muscles as well. Preliminary research on this topic indeed suggests negative effects of antipsychotic medication on spoken language, though it yet unclear whether these effects are caused by motoric or cognitive disturbances (Sinha, Vandana, Lewis, Jayaram, & Enderby, 2015a, 2015b). Furthermore, it has not been established whether these verbal communication disturbances should be regarded mostly as a symptom of psychosis or rather as secondary to antipsychotic medication use.

This study therefore aims to establish which components of language production (i.e. cognitive and/or motoric aspects) are affected by the psychotic disorder and which by the antipsychotic medication. We aim to dissociate the effects of dopaminergic medication from the symptomatology of schizophrenia spectrum disorders by comparing non-medicated patients with patients on antipsychotic medication on various aspects of their spontaneous language production. We further aim to assess the value of these language variables in predicting group status (patient versus control). Furthermore, by analyzing the effects of different types of

antipsychotic drugs based on their dopamine receptor profiles, we aim to shed light on the mechanisms behind the language disturbances caused by antipsychotic medication.

These aims are addressed by analyzing linguistic aspects of spoken language in which cognitive and motoric aspects of language can be disentangled. Cognitive aspects of language production are reflected in a person's speed in formulating sentences (i.e. by the ability of *formulating*). This can for instance be measured by looking at a person's 'speech rate'. Speech rate is of course determined by the speed at which you articulate speech (i.e. motor speed), but more importantly by the rate of retrieving words and sounds in your mental lexicon and the rate of building sentence plans, which leads to pauses in spoken language. 'Articulation rate' is a purely motoric measure since it depends only on (the control of) the vocal tract. Articulation rate is measured as the number of words produced only during the time the person is actually vocalizing (i.e. producing sounds). By pitting speech rate against articulation rate, one can distinguish between language disturbances (either cognitive or motoric in nature), and speech disturbances that are only motoric in nature.

Based on previous studies investigating language production in schizophrenia (Alpert, Rosenberg, Pouget, & Shaw, 2000; Cohen, Mitchell, & Elvevåg, 2014; Covington et al., 2005; DeLisi, 2001) we predict that patients with a schizophrenia spectrum disorder have a lower speech rate and articulation rate, pause more and speak a smaller percentage of time, than healthy controls. We further expect these measures to be associated with psychotic symptom severity since we assume them to be symptoms of schizophrenia spectrum disorders. Additionally, we hypothesize that antipsychotic medication only affects the motor stage of language production, that is articulation. This leads to the prediction that articulation rate is lower in patients who use dopamine antagonists, but that cognitive language measures remain

unaffected by antipsychotic drugs. Furthermore, we expect the articulation rate to be negatively associated with the amount of dopamine receptor binding.

Summarizing, language disturbances are a core symptom of schizophrenia spectrum disorders and may be a leading symptom in acute diagnosis. However, the disturbances we notice in medicated patients can either be a symptom of their disease, a side effect of their medication, or both. This study aims to disentangle the effects of antipsychotic medication from the disturbances that are characteristic to the disorder itself in order to fully assess language and/or speech disturbances as a symptom of psychosis.

2. Methods

2.1. Participants

A total of 101 participants, of which 59 patients with a schizophrenia spectrum disorder and 42 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, Flaum, & Arndt, 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. 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). Exclusion criteria were the presence of uncorrected hearing disabilities or speech deficits, such as excessive 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 Positive and Negative Syndrome Scale (PANSS)(Kay, Fiszbein, & Opfer, 1987). The PANSS is a scale used to assess the severity of psychotic symptoms, which takes around 45 minutes to administer. The symptoms it assesses are divided into three subsection; positive, negative and general symptoms of psychosis. Positive symptoms include hallucinations (i.e. perceptions without an external stimulus) and delusions (i.e. mistaken belief that is held with strong conviction). Negative symptoms include flattening of affect, reduced motivation and cognitive disturbances.

Depression, hypochondria and anxiety are among the general symptoms that occur in psychosis. This study was approved by the Ethical Review Board of the University Medical Center Utrecht. Informed consent was obtained from all participants. Participants received a small monetary award (ten euro).

2.2. Interview procedures

Semi-structured interviews varying from five to thirty minutes in length were obtained from participants by J.B. and A.V. and trained research interns. Average interview duration was fourteen minutes. Participants were informed that the research involved the analysis of 'general experiences' of patients as compared to healthy individuals. Participants were told only after completion of the interview that the research also focused on the way they speak. This procedure was used to elicit spontaneous speech. The interviewer refrained from speaking as much as possible, only encouraging the participants to elaborate on their answers. Interviews took place between December 2015 and March 2018.

A set of questions was used in the interview to control for potential variations in speech due to the topic that was discussed. All questions concerned 'neutral' general life experiences; that is, 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 the supplementary material (Table S1).

2.2.1. Recordings

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.

2.2.2. Speech processing

The digitized recordings were analyzed using the Praat sofware,(Boersma & Weenink, 2013) which is standardly used for acoustic analyses of speech. Speakers 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. Pauses were assigned to the speaker that started speaking after the pause. All speech segments per participants were recombined into a new audio file, which thus contained only the time that participant was speaking and pausing. Data files were blinded for diagnosis to prevent bias in separating the speaker. Inter-rater reliability for tier separation was 97.7 percent based on the outcome measures used in this current paper. All files were set to an average intensity of 60dB to avoid differences in the analyses based on speaking volume.

2.2.3. Speech variables

The ‘Praat Script Syllable Nuclei v2’(Quené, Persoon, & de Jong, 2011) was used to automatically obtain measures of speech and articulation rate. The output of this script includes the following raw numbers: total number of syllables and total number of pauses. A silence was counted as a pause if it lasted longer than 200ms, since shorter silences in speech can still be related to the producing of sounds such as plosives (e.g. the /p/, which introduces a short silence in the sound wave).(Rosen, 1992) The raw measures were adjusted for the total duration of the participants audio track, since they are strongly dependent on the exact length of the interview. This resulted in the following outcome measures: speech rate, articulation rate, average pause duration and the percentages of time speaking, articulating and pausing. A distinction was made between variables that describe only speech (motoric aspects of communication) and language variables in which cognitive processes also play a role. For an overview of language and speech variables, see Table 1.

Table 1. Description of language variables

Variable	Definition / calculation
Speaking time	Total time the participant was speaking in seconds. Equals the sum of phonation time and pause time. Equals the length of the participants audio track.
Pause time	Total time the participant was pausing in seconds. Equals speaking time – phonation time.
Phonation time	Total time the participant was producing speech sounds in seconds.
Percentage of time speaking	(speech time / total interview duration) *100.
Percentage of time articulating	(phonation time / total interview duration) * 100.
Percentage of time pausing	(pause time / total interview duration)*100.
Speech rate	Total number of syllables produced / speech time.
Articulation rate	Total number of syllables produced / phonation time.
Pause rate	Total number of pauses / speaking time.
Pauses per syllable	Total number of pauses / total number of syllables.
Pause time adjusted	Pause time / total interview duration.
Average pause duration	Pause time / number of pauses.

2.3. Classification of antipsychotics

The antipsychotic drugs were classified into two different categories based on their mechanism of action. Antipsychotic drugs are often categorized into two main classes, namely typical and atypical antipsychotis. Typical antipsychotics are older antipsychotics with strong affinity for the dopamine receptor, while atypical antipsychotics also interact with other receptors than the dopamine receptor. The dopamine D2 receptor is mostly targeted by antipscychotic drugs. Drugs such as clozapine and quetiapine bind more loosely to the dopamine D2 receptor than dopamine itself.(Seeman & Tallerico, 1998) By contrast, typical antipsychotics such as haloperidol and risperidone are 'strong' dopamine D2 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 D2 antagonist, though it also has some agonistic effects based on the cell type.(Shapiro et al., 2003) Patients were divided into three categories based on these different dopamine binding profiles, namely patients with 1) no antipsychotic drug, 2) low D2 receptor occupancy drugs (i.e. quetiapine, paliperidone, olanzapine and clozapine) or 3) high D2 receptor occupancy drugs (i.e. aripiprazole, risperidone, flupentixol, amisulpride and haloperidol)(Amato, Vernon, & Papaleo, 2018; Gerlach et al., 2003; Kapur & Seeman, 2001). Participants that used both a loosely and a tightly binding antipsychotic were categorized into the tightly binding group.

Antipsychotic drug dosages were recalculated into chlorpromazine equivalents to evaluate the effect of dosage between the drugs. Since Leucht's methods provide recalculations for more drugs than other methods do, these equivalents were used in the analyses (Leucht et al., 2014).

2.4. Data analysis

All analyses were performed in IBM SPSS Statistics version 22.0 for Windows. Participant characteristics were compared between groups using an analysis of variance (ANOVA) for continuous values, and a χ^2 test for categorical values. Between group analysis for speech features was obtained through a multivariate analysis of variance (MANOVA) by applying a general linear model. The MANOVA assumptions of linearity, normality and homoscedacity were checked visually by means of Q-Q plots and scatterplots of the residuals. Logistic regression analysis was performed to assess the value of the language variables as a predictor of group status (i.e. patient or healthy control). The Wald test for logistical regression was used for normally distributed data. A General Linear Model (GLM) was used to measure the effect antipsychotic medication on speech variables in the patient group only. Multiple Regression Analysis (MRA) was used to model the effect of different types of antipsychotics on articulation rate. A Jonckheere-Terpstra test was used to assess a trend in articulation rate in the three antipsychosis groups.

3. Results

Clinical and demographic data are shown in Table 2. The groups did not differ with regard to sex and age. Patients received less years of education than healthy controls, which is expected given that the first psychosis often occurs when people still receive education. There was no difference in parental years of education between groups.

Patients with a schizophrenia spectrum disorder and healthy controls were compared on variables of spontaneous speech using a MANOVA. To correct for the influence of age, gender and education level on normal variation in speech, all three variables were entered as covariates in the model. The MANOVA was statistically significant for group status, Pillai's trace F (9, 87) =3.384, p =.001, partial η^2=.259. No significant effects were found for age, sex and years of education. Separate analyses of the dependent variables showed significant corrected effects for psychotic diagnosis on speech rate, articulation rate and percentage of time speaking (see Table 3).

Table 2. Demographic characteristics

Variable	Psychotic patients (n = 59)	Healthy controls (n = 42)	p-value
Sex, male : female	44 : 15	38 : 4	.069
Age, mean ± SD	30.5 ± 10.66	31.4 ± 11.54	.692
Years of education, mean ± SD	12.9 ± 2.71	14.8 ± 2.14	<.0001
Parental years of education, mean ± SD	12.5 ± 2.76	12.7 ± 3.13	.717
Duration of illness years, mean ± SD	5.9 ± 8.10	-	-
Total PANSS, mean ± SD	52.1 ± 12.37	-	-
Psychotic disorder, n (%)			
Schizophrenia	19 (32.2)		
Schizoaffective disorder	8 (13.6)		
Schizophreniform disorder	3 (5.1)		
Psychosis NOS	29 (49.2)		
Antipsychotic medication, n (%)[a]			
No antipsychotic medication	5 (8.5)		
Antipsychotic medication			
Amisulpride	2 (6.3)		
Aripiprazole	19 (32.2)		
Clozapine	9 (15.3)		
Flupentixol	2 (3.4)		
Haloperidol	3 (5.1)		
Lurasidone	1 (1.7)		
Olanzapine	8 (13.6)		
Paliperidone	6 (10.2)		
Risperidone	4 (6.8)		
Quetiapine	5 (8.5)		
Chlorpromazine equivalent (mg), mean ± SD	429.7 ± 283.63		

Table legend: SD = standard deviation,. n = sample size

[a] Five patients used aripiprazole, risperidone or quetiapine in addition to another antipsychotic, therefore, numbers and percentages add up to 59 and percentages to over 100%.

Table 3. Language characteristics of patients and healthy controls

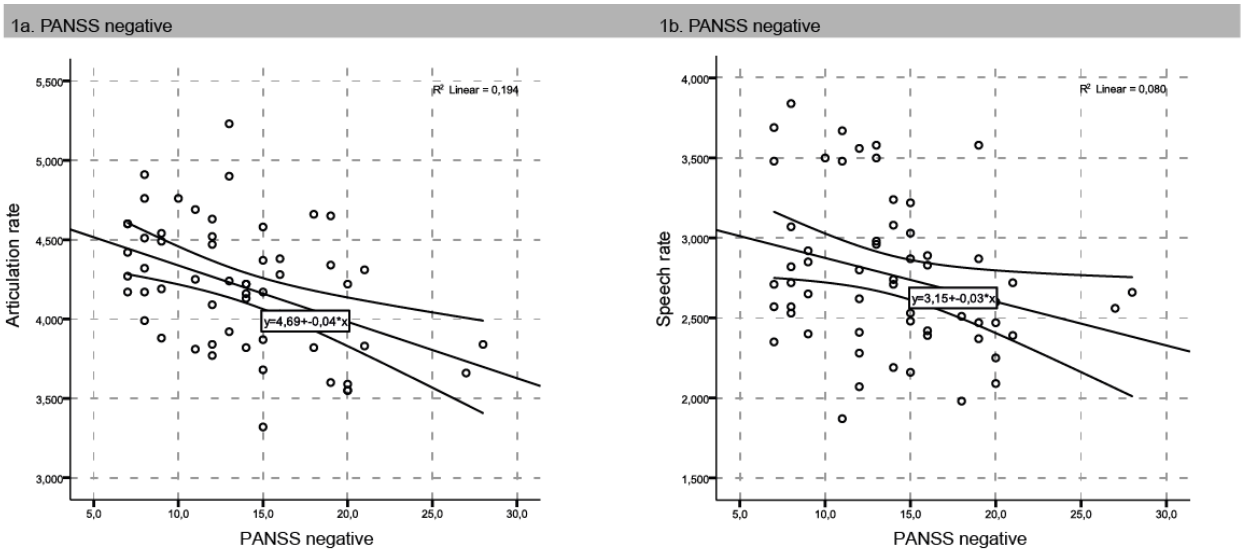
Variable	Psychotic patients (N = 59)	Healthy controls (N = 42)	p-value
Percentage of time speaking, mean ± SD	70.6 ± 10.47	79.9 ± 7.14	<.0001**
Percentage of time articulating, mean ± SD	46.8 ± 10.25	56.5 ± 8.65	<.0001**
Percentage of time pausing, mean ± SD	24.9 ± 6.52	23.7 ± 5.44	.237
Speech rate, mean ± SD	2.8 ± .48	3.2 ± .40	<.0001**
Articulation rate, mean ± SD	4.2 ± .40	4.5 ± .35	<.0001**
Pause rate, mean ± SD	.33 ± .051	.32 ± .044	.198
Pause time adjusted, mean ± SD	.34 ± .087	.29 ± .070	.002**
Pauses per syllable, mean ± SD	.12 ± .033	.10 ± .024	.001**
Pause duration, mean ± SD	1.02 ± .235	.92 ± .172	.004**

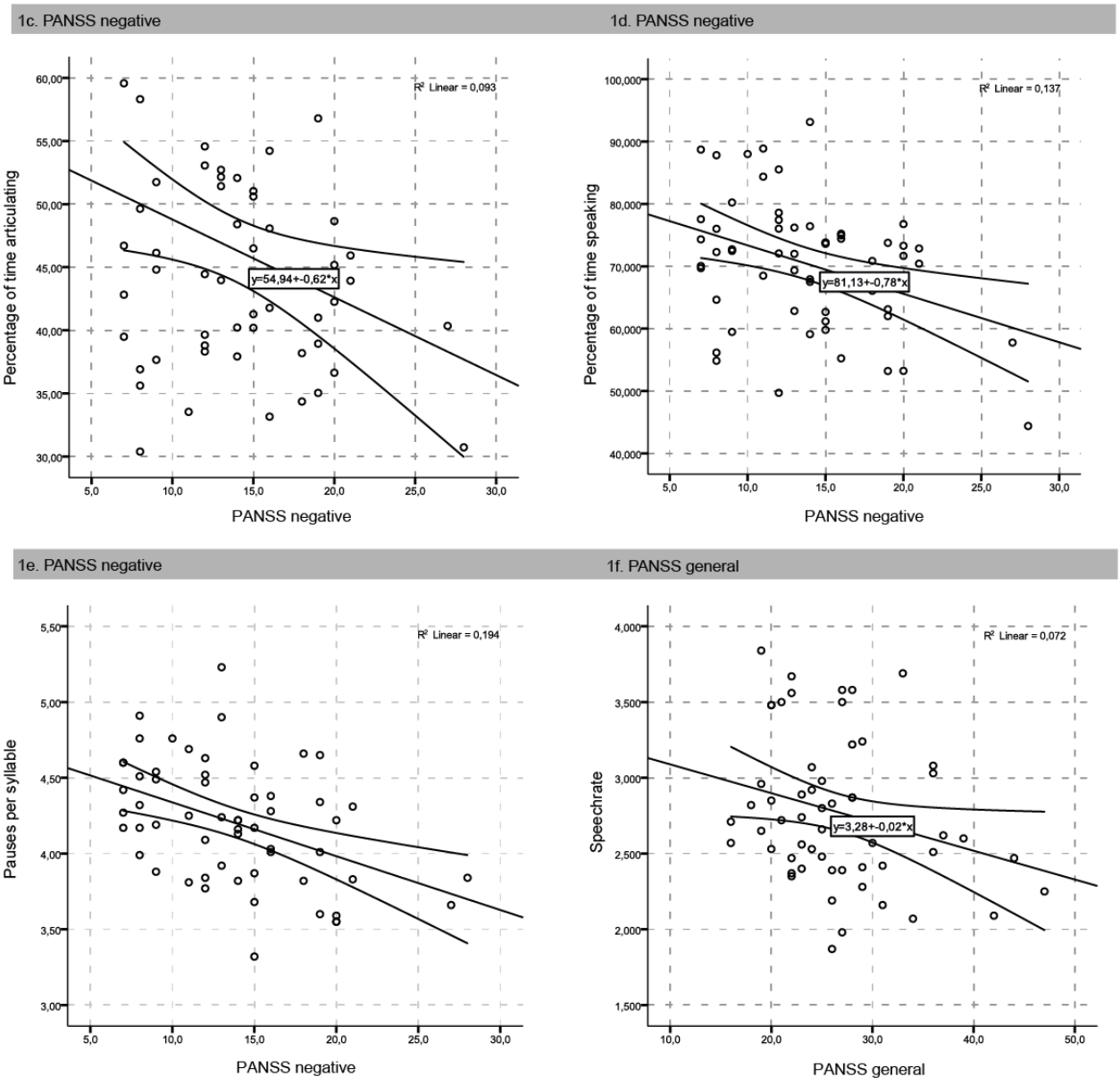
Covariates included in the model: age and years of education. Table legend: ** significant at the level of α = .01. SD = standard deviation. For explanation of the language variables, see Table1.

To assess to what extent language measures were able to predict group status, a forward binary logistic regression was conducted. Language measures, age, years of education and gender were entered as covariates into the model. On step 1, only percentage of time speaking was entered into the equation, which explained 31.3% of the variation (χ^2 =22.956, p < .00001, Nagelkerke R^2= .313). Speech rate was added on step 2, which improved the variation explained by the model to 36.1%. Based on these language variables alone, patients with a schizophrenia spectrum disorder and healthy controls could be identified ('diagnosed') with a sensitivity of 73.9% and a specificity of 70.0%. Adding years of education at step 3 improved the variation explained by the model to 41.3%, and increased diagnostic accuracy, as the sensitivity went up to 78.3% and specificity to 75.0%.

In order to evaluate language measures as a symptom of psychosis, the relation with PANSS scores was assessed by means of correlation analyses. PANSS positive did not correlate significantly with any of the speech measures (all p >.05). PANSS general revealed a significant correlation with speech rate (r =-.268, p =.042). PANSS negative revealed medium to large negative correlations with articulation rate (r =-.441, p =.001), speech rate (r =-.284, p =.031), percentage of time speaking (r =-.371, p =.004), phonating (r =-.306, p =.020), and the number of pauses per syllable (r =.273, p =.004). See Figure 1a-f.

Figure 1 a-f. Relation between PANSS scores and language variables. Language and speech variables are displayed on the y-axes, with PANSS negative or general scores on the x-axes. Dots represent individual cases. Lines display linear fitted models, 95% confidence intervals of the means are displayed.





A general linear model was used to assess the relation between language characteristics, psychotic symptoms and the use of antipsychotic medication. Only language variables that differed between healthy controls and patients were included in the analyses. Negative PANSS, years of education and duration of illness were entered as covariates, with antipsychotic drug use as a fixed factor. No significant effects were found for either years of education (Pillai's trace =.151, p =.399) or duration of illness (Pillai's trace =.146, p =.430). PANSS negative was a

significant predictor of overall language variables (F (7, 42) =2.493, p =.031, partial η^2 =.294). The use of antipsychotic medication did not significantly predict overall language variables (p =.059). Analysis of the dependent variables separately revealed that the use of antipsychotics was a significant predictor for articulation rate (F (1,48) = 4.501, p =.039, partial η^2 =.086) but not for other language variables (all p>0.1).

To further explore the relation between articulation rate and the use of antipsychotics, additional analyses were performed to explore this mechanism. Therefore, the effect of different types of antipsychotics (low or high D2 receptor occupancy) was assessed by means of a regression model. Articulation rate was entered as the dependent variable, drug type (low or high receptor occupancy), years of education, duration of illness and PANSS subscales were entered as predictors in a forward Multiple Regression Analysis (MRA), see Table 4.

Table 4. Predictors of articulation rate in patients with a schizophrenia spectrum disorder

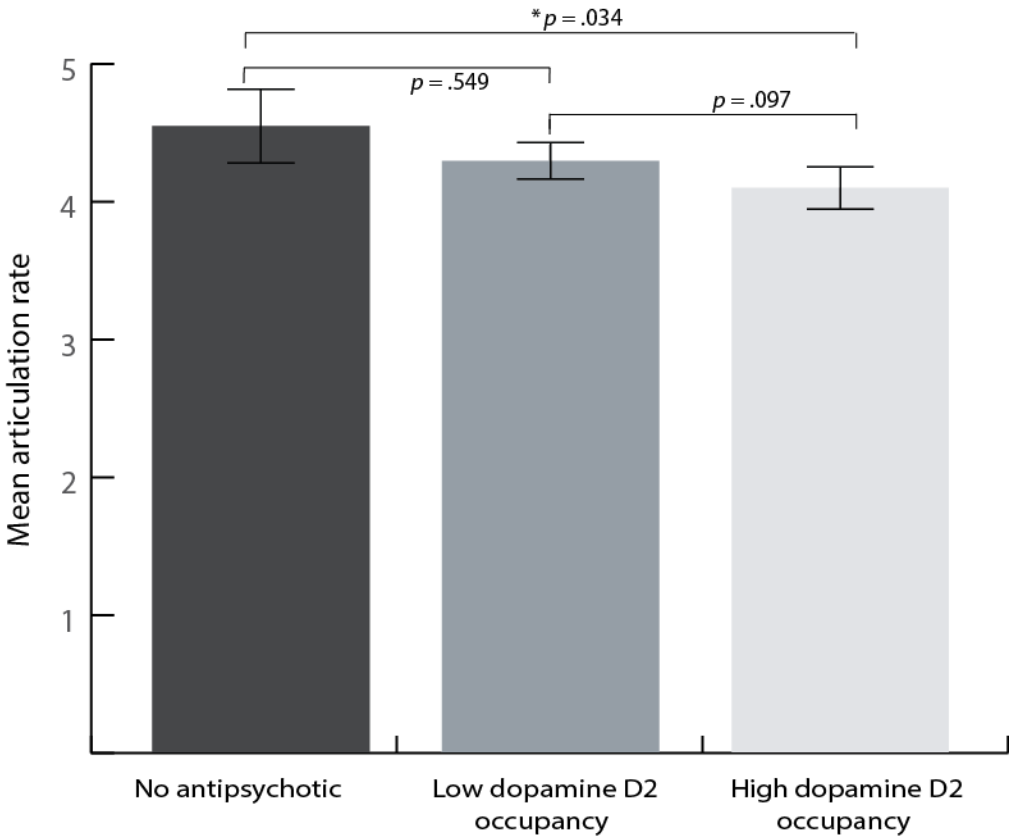
	B	SE B	β	*p*-value
Step 1[a]				
Constant	4.694	.142		<.0001**
PANSS negative	-.036	.010	-.439	.001**
Step 2[b]				
Constant	4.817	.144		<.0001**
High D2 receptor accupancy	-.239	.091	-.301	.011*
PANSS negative	-.036	.009	-.447	<.0001**

Note: adjusted R^2= .184 for step 1 and adjusted R^2= .263 for step 2

[a] Predictors excluded from model: General and Positive PANSS, D2 receptor profile, age, years of education. [b] Predictors excluded from model: General and Positive PANSS, D2 receptor profile, age, years of education. Table legend: * significant at the level of α = .05, ** significant at the level of α = .01. SE =standard error.

On step 1 of the MRA, PANSS negative accounted for a significant 18.4% of the variation in articulation rate, F (1,55) =13.656, p =.001. The use of strong dopamine D2 receptor antagonists were added on step 2, which accounted for an additional 7.9% of the variation in articulation rate, F (2, 54) =11.009, p <.0001. Combined, the predictors accounted for 26.3% of the variance in articulation rate. The Jonckheere-Terpstra test revealed a significant trend in articulation rate over the antipsychotic groups (p =.005) ordered from no, to low and to high dopamine D2 receptor affininity, see Figure 2.

Figure 2. Relation between type of antipscyhotic medication and articulation rate. Error bars are two times the standard error. * Indicates significance at the level of α =.05.



4. Discussion

This study investigated the influence of antipsychotic medication on spoken language production in patients with a schizophrenia spectrum disorder. Verbal communication disorders are a well-known symptom of psychotic disorders, while at the same time antipsychotic medication impacts the language of these patients as well.

A comparison with healthy controls was made to analyze whether the patient group showed deviations from healthy controls in their spoken language. As predicted, regardless of the type of medication they use, schizophrenia patients produced significantly fewer words per minute and articulated slower than healthy controls, as shown by fewer syllables per minute, less phonation time and a significant lower percentage of time speaking during the interview.

We aimed to disentangle the side-effects of antipsychotic medication from the language disturbances that are considered to be a symptom of psychosis. Our results indicate that antipsychotic medication only affects motoric aspects of speech (i.e. articulation), resulting in a reduced articulation rate (i.e. the speed at which speech sounds are produced while a person is actually phonating). Antipsychotic medication thus induces *disordered speech*. The effect of schizophrenia spectrum disorders proper on verbal communication is both cognitive and motoric in nature and are thus best characterized as *language disturbances,* reflected by reduced speech rate, articulation rate and a reduced overall language output.

The difference between language disorders as a psychotic symptom and the effect of medication on speech was further examined by dividing the patient group into those without medication, those with presumed high D2 receptor occupancy and those with presumed low D2 receptor occupancy. These analyses revealed that tightly binding dopaminergic drugs have a

stronger effect on articulation than loosely binding drugs. The degree of dopamine receptor occupancy thus predicts articulation rate to a large extent, which hints at a causal relation between blockage of the dopamine receptor blockage and articulation. This is an important finding, as reduced articulation speed can be a social handicap, especially when speech velocity is already low.

Further analyses of the symptomatology revealed that negative symptom severity is negatively associated with reduced speech rate, articulation rates and the amount of time someone speaks, which is also to be expected. PANSS general scores were negatively associated with articulation rate. This clearly suggests that speech production can be used a (crude) reflection of psychopathology, signaling both general and negative symptoms, but not psychotic symptoms. That wew did not find associations between positive PANSS scores and verbal communication disorders in this study could in part be due to the type of analyses we performed. Only paralinguistic measures that analyze the amount and speed of language production were used in this study, instead content and incoherent structure of the language might be disturbed in patients with more positive psychotic symptoms. Further research should therefore incorporate analyses that estimate the internal coherence and content of the speech to assess language disorders in pscyhosis from a different angle.

The paradox of dopaminergic drugs

An apparent contrast that arises in this line of research is that dopamine dysregulations are thought to underlie the language disturbances in schizophrenia spectrum disorders, while we further argue that antipsychotic drugs targeting dopamine dysregulations cause yet other disturbances in language production. This paradox is less surprising if we acknowledge that the

dopamine hypothesis can be seen as somewhat paradoxical itself. The dopamine hypothesis has been adapted several times; in its current form it proposes that several developmental, genetic and environmental 'hits' lead to a dysregulation of the presynaptic dopamine system (Howes & Kapur, 2009). Several extensions of this theory suggest that positive symptoms emerge because of the abnormal release of dopamine, which leads to aberrant salience. Negative symptoms may evolve from the increased volatility of the dopamine system, which leads to 'drowning out' of actual stimuli of reward (Roiser et al., 2009). Dopamine dysregulations underlying psychosis are thus thought to be both caused by an excess as well as a shortage of dopamine. Perhaps antipsychotic drugs have a similar effect; while they can reduce an excess of dopamine in some brain tissues, they may increase shortages in other tissues, which could cause speech disturbances.

Strengths and limitations

There is a long history of investigating language disturbances in schizophrenia spectrum disorders, however, to this date little was known about the effects of antipsychotic medication on verbal communication in this patient group. Given that language disturbances a highly important source of information in the diagnostic process, it is good to realize that a slower articulation rate in medicated patients is not so much a symptom of psychosis, but rather an effect of the medication. Instead, reduced production of language and a slower speech rate are a reflection of negative and general symptoms.

Even though the measures used in the current research are rather general and might not be specific to psychotic disorders alone, we were able to discriminate between psychotic patients and healthy controls with reasonable sensitivity and specificity. These results hold a promise for

future research, which should aim to develop linguistic measures that are more specific to psychotic disorders, in order to improve specificity and develop speech analysis as a diagnostic asset.

While our analyses revealed large effects, the relatively small sample size may reduce generalizability to future research. Especially the number of patients who did not use any antipsychotic drugs was limited. Furthermore, the collection and analyses of spoken language is a time-consuming procedure, which also leads to smaller sample sizes. In our analyses we only investigated effects of dopaminergic medication, however, many antipsychotics also block the serotonin receptor. Though it is not expected that the serotonin receptor would influence language production as much as dopamine does, it would be interesting for future research to include other receptor profiles in analyses. A larger sample of patients would also allow a more fine-tuned relation between language characteristics as well as antipsychotic medication use.

It is important to gain insight into language disorders in this patient group, since language obviously is of primary importance for social relations and daily interactions.(Sinha et al., 2015b) Disturbances in spontaneous speech can therefore have a negative impact on a broad range of life-experiences. With this study, aspects of the impact of medication used by schizophrenia patients on speech are brought into view.

Conclusions

Language characteristics are a valid tool to assess symptom severity in psychotic disorders and could prove useful in early stages of the diagnostic process. Furthermore, antipsychotic medication has a negative effect on motoric aspects of language production (articulation), but no evidence was found for an impact on cognitive processes underlying language production. These

findings call for a correct use of the terms ‘speech’ and ‘language’ disorder, since antipsychotic medication induced a speech (i.e. articulation) effects, while schizophrenia spectrum disorders proper are characterized by language disorders. Both psychiatrists and patients should be aware of this negative side effect of medication with high D2 receptor occupancy, in order to evaluate both the symptomatology and iatrogenic effects of medication on spoken language.

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Supplementary Material

Table S1. Questions used in the semi-structured interview

1	Kun je vertellen over je zwemles van vroeger? Hoe vond je dat? Wat vond je het moeilijkst? En het leukst? *Can you tell about your swimming lesson from when you were young? How did you like it? What did you find the most difficult? And what did you like the best?*
2	Kun je vertellen over je tandartservaringen (slechte en goede ervaringen)? Kun je bijvoorbeeld vertellen over de laatste keer dat je bent geweest? En hoe heb je dat als kind ervaren? *Can you tell about your dentist experiences (bad and good experiences)? For example, can you tell me about the last time you've been? And how did you experience going as a child?*
3	Heb je een rijbewijs? Zo ja, kun je wat vertellen over hoe de lessen gingen en hoe het examen ging? *Do you have a driving license? If so, can you tell me how the lessons went and how the exam went?*
4	Ben je wel eens in een pretpark geweest? Kun je daar wat over vertellen? Heb je een favoriet pretpark, vertel daar eens over? Waarom is het je favoriete park? *Have you ever been to an amusement park? Can you tell me about that? Do you have a favorite amusement park, tell me about it? Why is it your favorite park?*
5	Naar welke Nederlandstalige Tv-programma's kijk je vaak? En aan welke heb je een hekel? Waarom? *Which Dutch TV shows do you often watch? And which do you hate? Why?*
6	Kijk je wel eens naar sport, zoals voetbalwedstrijden? Zo ja, naar welke wedstrijden en wat vind je daarvan? En ben je een fan van een bepaalde club of sporter? *Do you ever watch sports, like football matches? If so, what matches and what do you think about it? And are you a fan of a particular club or athlete?*
7	Kun je je laatste droom beschrijven? *Can you describe your last dream?*
8	Hoe was je laatste verjaardag? Hoe vier je normaal je verjaardag?

How was your last birthday? How do you usually celebrate your birthday?

9 Wat zou je doen als je een miljoen zou winnen?
What would you do if you were to win a million?

10 Als je voor altijd een bepaalde leeftijd kon hebben, welke leeftijd zou dat dan zijn? Waarom?
If you could have a certain age forever, what age would it be? Why?

11 Als je overal ter wereld heen mocht, waar zou je heengaan?
If you could go anywhere in the world, where would you go?

12 Welk klusje in huis vind je echt vreselijk om te doen? Waarom? Doe je het dan?
What kind of household chore do you really hate? Why? Do you do it then?

13 Ga je wel eens op vakantie? Wat is je favoriete vakantiebestemming? Waarom?
Do you go on vacation? What is your favorite vacation destination? Why?

14 Welke oorlog in de geschiedenis heeft indruk op je gemaakt? Waarom?
What war in history has impressed you? Why?

15 Wat voor werk doen/deden je ouders?
What kind of work do your parents / did your parents do?

16 Wat voor werk doe je/heb je recent gedaan? Wat sprak je daarin aan?
What kind of work do you / have you done recently? What did you talk about?

17 Kun je wat vertellen over je laatste sollicitatiegesprek? Was je zenuwachtig? Ben je aangenomen?
Can you tell me about your last job interview? Were you nervous? Were you hired?

18 Wat is je favoriete jeugdherinnering? Wie waren erbij? Waarom vind je dat zo'n fijne herinnering?
What is your favorite childhood memory? Who were there? Why do you think that's a nice memory?

19 Hoe werden bij jou thuis de feestdagen gevierd?
How did you celebrate the holidays back home?

20 Waar ben je geboren? Welke stad, ziekenhuis of thuis? Wie waren daarbij?
Where were you born? Which city, in hospital or at home? Who were there?

21 Wat voor soort kind was je toen je klein was?
What kind of child were you when you were small?

22 Had je vroeger een lievelingsknuffel? Of iets anders dat je altijd bij je wilde hebben?
Did you have a favorite toy when you were young? Or something else that you always wanted to have with you?

23 Wat was je favoriete boek toen je klein was? En waarom was je daar zo dol op?
What was your favorite book when you were small? And why were you so fond of it?

24 Lijk je op je ouders? Op wie lijk je het meest, waarom?
Do you look like your parents? Who do you resemble the most, why?

25 Heb je broers of zussen? Op wie lijk je het meest, waarom? Met wie had je het meest ruzie?
Do you have any brothers or sisters? Who do you resemble the most, why? Who did you argue with most?

26 Wat wilde je vroeger worden (wat voor baan)? Heb je dat lang gedacht? Zou je dat nu nog willen?
What did you want to become when you were young (what kind of job)? Did you want that for a long time? Would you still like that?

27 Heb je wel eens een huisdier gehad? Zou je een huisdier willen? Wat voor een? Hoe was je band daarmee?
Have you ever had a pet? Would you like a pet? What kind? How was your relationship with it?

28 Welke mensen waren belangrijk voor je in je jeugd? Waarom?
What people were important to you in your youth? Why?

29 Was je weleens ziek als kind? Heb je weleens in het ziekenhuis gelegen?
Were you sometimes sick as a child? Have you ever been to the hospital?

30 Wat was je favoriete eten toen je klein was?
What was your favorite food when you were small?

31 Wat deed je vroeger waardoor je in de problemen kwam? Werden je ouders dan boos?
What did you do in the past that caused you to get into trouble? Did your parents get angry?

32 Wat voor spellen speelde je vroeger? Waar speelde je meestal? Buiten/binnen? Met wie?
What games did you play when you were young? What did you usually play? Outside inside? With whom?

33 Kun je je de laatste keer herinneren dat je goed nieuws kreeg? Wat voor nieuws was dat? Wat voor effect had dat op je?
Can you remember the last time that you got good news? What kind of news was that? What effect did that have on you?

34 Hoe heb je je beste vriend/in ontmoet?
How did you meet your best friend?

35 Ben je wel eens verliefd geweest? Weet je nog hoe jullie in gesprek kwamen? Was je verlegen? Weet je nog hoe jullie eerste afspraakje was? Was je zenuwachtig?
Have you ever fallen in love? Do you still know how you got talking? Were you shy? Do you remember how your first date was? Were you nervous?

36 Wat zijn belangrijke momenten in je leven geweest?
Looking back, what were important moments in your life?

37 Welke mensen spelen nu een belangrijke rol in je leven? Waarom?
Which people now play an important role in your life? Why?

38 Wat was een van de beste feestjes waar je ooit bent geweest?
What was one of the best parties you've ever been to?

39 Als je een tijdmachine had, naar welke tijd in de toekomst/verleden zou je gaan? Waarom?
If you had a time machine, what time in the future / past would you go? Why?

40 Als je met één persoon op aarde nu mocht spreken, met wie zou dat zijn?
If you were to speak to one person on earth, who would that be?

41 Als je een dier was, welk dier zou je dan zijn en waarom?
If you were an animal, what animal would you be and why?

42 Wat is je favoriete bezigheid in de zomer? Waarom?
What is your favorite activity in the summer? Why?

43 Stel je wordt gedropt op een onbewoond eiland en moet daar een jaar blijven, welke 3 dingen zou je dan meenemen?
Imagine being dropped on an uninhabited island and staying there for a year, what 3 things would you bring?

44 Als je één van je zintuigen op moest geven welke zou het dan zijn? (horen, zien, voelen, ruiken of proeven) Waarom?
If you had to give up one of your senses, what would it be? (hear, see, feel, smell or taste)

Why?

45 Wat is het leukste cadeau dat je ooit hebt gekregen? Van wie kreeg je het?
What is the best gift you ever received? Who did you get from?

46 Wat is je favoriete stripfiguur? Waarom die?
What is your favorite cartoon character? Why that one?

47 Wat is het beste/leukste dat je deze week is overkomen?
What is the best / fun thing you have come across this week?

48 Wat is het vreemdste dat je ooit hebt gegeten? (bv. slak, oester)
What is the strangest thing you have ever eaten? (e.g. snail, oyster)

49 Als je vandaag één wereldprobleem mocht oplossen, welk probleem zou dat zijn? Waarom?
If you could solve one world problem today, what problem would that be? Why?

50 Als je nu een auto mocht kopen, wat voor auto zou dat dan zijn?
If you were to buy a car, what kind of car would it be?

51 Wat voor soort huis is je droomhuis? Waar zou dit huis staan? Met wie zou je er willen wonen?
What kind of house is your dream home? Where would this house be? Who would you like to live with?

52 Welke taal zou je nog willen leren spreken? Waarom deze taal?
What language would you still like to learn? Why this language?

53 Als je voor één dag God zou zijn, wat zou je dan doen?
If you could be God for one day, what would you do?

54 Hoe ziet jouw perfecte pizza eruit? Wat zit er allemaal op?
What does your perfect pizza look like? What's on it?

55 Wat is het raarste kledingstuk dat je ooit hebt gedragen?
What's the strangest piece of clothing you've ever worn?

56 Wat zou je doen als je een dag onzichtbaar zou kunnen zijn?
What would you do if you could be invisible one day?

57 Van welk beroep droomde je als kind? Wat trok je hier toen aan aan?
What profession did you dream of becoming as a child? What did you like about it?

58 Als je getuige zou kunnen zijn van elke gebeurtenis in het verleden, heden of toekomst,

welke zou het dan zijn?

If you could witness any event in the past, present or future, what would it be?

59 Als je elke willekeurige fictieve persoon zou kunnen zijn, wie zou je dan kiezen?

If you could be any fictional person, who would you choose?

60 Als je uit iedereen in de wereld kon kiezen, met wie zou je dan uit eten willen?

If you could choose from anyone in the world, who would you like to have dinner with?

61 Heb je liever een privévliegtuig of een privé-eiland? En waarom?

Would you rather have a private plane or a private island? And why?

Note: the original Dutch sentences are presented first, with the English translations in italics below.