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Priming production: Neural evidence for enhanced automatic semantic activity preceding language production in schizophrenia

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ABSTRACT

Introduction: Lexico-semantic disturbances are considered central to schizophrenia. Clinically, their clearest manifestation is in language production. However, most studies probing their underlying mechanisms have used comprehension or categorization tasks. Here, we probed automatic semantic activity prior to language production in schizophrenia using event-related potentials (ERPs).

Methods: 19 people with schizophrenia and 16 demographically-matched healthy controls named target pictures that were very quickly preceded by masked prime words. To probe automatic semantic activity prior to production, we measured the N400 ERP component evoked by these targets. To determine the origin of any automatic semantic abnormalities, we manipulated the type of relationship between prime and target such that they overlapped in (a) their semantic features (semantically related, e.g. "cake" preceding a < picture of a pie > , (b) their initial phonemes (phonemically related, e.g. "stomach" preceding a < picture of a starfish >), or (c) both their semantic features and their orthographic/phonological word form (identity related, e.g. "socks" preceding a < picture of socks >). For each of these three types of relationship, the same targets were paired with unrelated prime words (counterbalanced across lists). We contrasted ERPs and naming times to each type of related target with its corresponding unrelated target.

Results: People with schizophrenia showed abnormal N400 modulation prior to naming identity related (versus unrelated) targets: whereas healthy control participants produced a smaller amplitude N400 to identity related than unrelated targets, patients showed the opposite pattern, producing a larger N400 to identity related than unrelated targets. This abnormality was specific to the identity related targets. Just like healthy control participants, people with schizophrenia produced a smaller N400 to semantically related than to unrelated targets, and showed no difference in the N400 evoked by phonemically related and unrelated targets. There were no differences between the two groups in the pattern of naming times across conditions.

Conclusion: People with schizophrenia can show abnormal neural activity associated with automatic semantic processing prior to language production. The specificity of this abnormality to the identity related targets suggests that that, rather than arising from abnormalities of either semantic features or lexical form alone, it may stem from disruptions of mappings (connections) between the meaning of words and their form.

1. Introduction

Schizophrenia has long been characterized as an abnormality of semantics — a breakdown in the extraction and production of meaningful relationships (Bleuler, 1911/1950). Clinically, semantic abnormalities are most prominent in the disorganized speech produced by some patients (positive thought disorder, Andreasen and Grove, 1986; Elvevåg et al., 2007; McKenna and Oh, 2005). However, most cognitive and neuroscientific evidence for semantic abnormalities in schizophrenia comes from studies of language comprehension (Kuperberg, 2010a, 2010b; Kuperberg et al., 2009). In the present study, we report for the first time that people with schizophrenia show abnormal neural activity associated with automatic semantic processing prior to producing words. Moreover, we specifically link this abnormality to dysfunction of the mappings (connections) between the meaning of words and their form.

The most common way in which semantic processing has been studied in schizophrenia is using the semantic priming paradigm. The behavioral semantic priming effect describes the faster time it takes to recognize, read, or classify a target word that is preceded by a

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semantically related (versus unrelated) prime word (Meyer and Schvaneveldt, 1971; Neely, 1991). Electrophysiologically, the effect manifests as a relative reduction in the amplitude of the N400 event-related potential (ERP) — a waveform that peaks at approximately 400 ms after stimulus onset and that is sensitive to the ease of accessing the semantic properties of that stimulus (Kutas and Federmeier, 2011). When experimental conditions discourage strategic top-down mechanisms (e.g. when the time interval between the onset of the prime and the target — the Stimulus Onset Asynchrony, SOA — is very short), the semantic priming effect is driven primarily by automatic mechanisms: the prime automatically pre-activates semantic features of the target word, facilitating semantic processing of the target when it is presented.

If the prime and the target are directly semantically associated and/or share common semantic features, the magnitude of the automatic semantic priming effect in people with schizophrenia is usually same as in healthy controls (e.g. Barch et al., 1996; Blum and Freides, 1995; Chapin et al., 1992; Ober et al., 1995; Vinogradov et al., 1992). This suggests that the automatic activation of semantically related words in schizophrenia is normal. If, however, the relationship between the prime and target is indirect, the automatic semantic priming effect can be larger in people with schizophrenia than in healthy controls, particularly in patients with positive thought disorder (Kreher et al., 2009; Moritz et al., 2001; Moritz et al., 2003; Spitzer et al., 1993; Weisbrod et al., 1998)). This has been taken as evidence for an abnormally *broad* spread of automatic activity across semantic memory in schizophrenia.

Although the automatic semantic priming paradigm has yielded important insights, it has two major limitations. First, because it only manipulates the semantic relationship between the prime and the target, it primarily probes disturbances within semantic memory itself. However, there are alternative accounts of how automatic semantic abnormalities might arise in schizophrenia. One possibility is they stem from disturbances of lower-level perceptual representations that propagate up to influence semantic processing (see Javitt, 2009; Leitman et al., 2010). Another possibility is that they stem from noisier *connections* between a word's semantic features and its lexical form.[1] This account assumes a connectionist-type architecture (cf. Rumelhart et al., 1986), in which our knowledge of a particular word is encoded as the strength of connections between processing elements that represent its sensory properties and its meaning (e.g. Dell et al., 1999; Grainger and Holcomb, 2009, see figures in the Discussion). For example, our knowledge of the word, “boy”, its specific orthographic form (b-o-y) and its specific sound (/bɔɪ/) are conceptualized as connecting strongly and precisely to a particular set of semantic features that characterize a boy (e.g. < male > , < young > , < human >). In schizophrenia, these connections may be weaker and less finely-tuned than in healthy adults. For example, the connections between b-o-y or /bɔɪ/ may be more weakly connected to a broader set of semantic features (e.g. < male > , < female > , < young > , < old > , < human >).

The second main limitation of using the traditional semantic priming paradigm to probe automatic semantic disturbances in schizophrenia is that it does not directly index language production. Rather, it requires participants to recognize, read, or categorize target words whose orthographic or phonological forms are provided by the bottom-up input. However, as noted above, the clearest *clinical* manifestation of semantic dysfunction in schizophrenia is in language production — the symptom of positive thought disorder (Andreasen and Grove, 1986). Therefore, a paradigm that requires participants to actually *produce* target words might provide a more sensitive measure of any underlying semantic abnormality.

Importantly, the effects of introducing a related prime word can be quite different in production tasks from categorization/recognition tasks. Whereas a related (versus an unrelated) prime word will usually facilitate the recognition or categorization of a target word, it can actually interfere with producing the name of a target picture. This interference effect can be explained by connectionist theories, particularly those that posit close relationships between language comprehension, production and adaptation (e.g. Dell and Chang, 2014; Oppenheim et al., 2010). According to such theories, each time a word is processed (comprehended or produced), the connections between its semantic features and its lexical form are strengthened — adaptation. This means that if a participant has just strengthened connections between the semantic and form properties of a prime word, then these connections can compete when she comes to strengthen connections between the semantic features and lexical form of a related target word, ahead of its production. The costs of inhibiting these competing connections can outweigh any facilitatory effects, leading to an interference effect.

The present study aimed to address these drawbacks of the classic semantic priming paradigm. We probed automatic semantic processing ahead of word production — picture naming — by measuring the amplitude of the N400 component, time-locked to the onset of a target picture. In this type of naming task, the N400 is often assumed to capture activity associated with mapping the target's semantic features on to its lexical form, prior to production (Chauncey et al., 2009; Koester and Schiller, 2008; see Blackford et al., 2012, pp. 96–97 for a detailed discussion). Importantly, it can be measured without significant contamination of articulation artifact.

In order to probe the origins of any automatic semantic abnormalities in schizophrenia, we used a paradigm that we have previously developed in young healthy controls (Blackford et al., 2012). Each target picture was immediately preceded by a prime word, and we manipulated the relationship between the prime and target such that they overlapped in (a) their semantic features, (b) their phonemic properties (sharing the same initial phonological segment), or (c) both their semantic features and their lexical form. For each of these three types of relationships, the same targets were paired with unrelated prime words, which were counterbalanced across lists, see Fig. 1. In all cases, the prime word was preceded by a forward mask, and the SOA between prime and target was very short (60 ms), ensuring that the effects of the prime on the target reflected automatic processes. We asked three questions:

1. Do automatic semantic disturbances prior to language production in schizophrenia stem from a primary disturbance within semantic memory?

To address this question, we compared ERPs and naming times to target pictures that were preceded by semantically related prime words (e.g. < picture of a pie > preceded by “cake”) with target pictures preceded by semantically unrelated prime words (e.g. < picture of a pie > preceded by “chalk”), see Fig. 1A. In healthy individuals, a semantically related (versus unrelated) prime leads to a reduction in the amplitude of the N400 evoked by the target, but to a longer time to name the target — behavioral interference (Blackford et al., 2012). The N400 priming effect is thought to result from an automatic pre-activation of the target's semantic features by the semantically related prime. This pre-activation makes it easier for producers to access these semantic features and begin to map them on to the lexical form of the target prior to its production. The behavioral interference effect is the classic picture-word semantic interference effect (Alario et al., 2000; Lupker, 1979; Rosinski, 1977). It occurs at a slightly later stage of processing, following the N400 time window when lexical selection is complete (Blackford et al., 2012). Within the type of connectionist

[1] By *lexical form*, we refer to a representation of a whole word that lies in between its semantic properties and its individual phonemes/letters. There is debate about the precise nature of this intermediate-level representation. In some models of word recognition (e.g. Grainger and Holcomb, 2009) and word production (e.g. Caramazza, 1997; Starreveld and La Heij, 1996), it is conceptualized as the full orthographic or phonological form of a word (the full set of letters or the particular sound associated with that word). In other models of language production, it is conceptualized as a more abstract (non-modality-specific) whole-word representation — the ‘lemma’ (Levelt, 1993).

Word-Picture Relationship		Context Word	Picture Target	Length (Target)	# Phonemes	# Syllables	Log Freq.
A. Semantic							
	Related	cake		5.7 (1.8)	4.7 (1.5)	1.7 (0.7)	8.1 (1.3)
	Unrelated	chalk					
B. Phonemic							
	Related	stomach		6.0 (2.0)	4.9 (1.8)	1.8 (0.7)	7.9 (2.0)
	Unrelated	ball					
C. Identity							
	Related	socks		5.8 (2.2)	4.6 (1.7)	1.7 (0.8)	7.9 (1.9)
	Unrelated	waffle					

Fig. 1. Example of word-picture stimuli pairs. Stimuli consisted of a prime word that was related to a target picture along one of three types of relationships: Semantic, Phonemic Onset, or Identity. For each Relationship Type, an Unrelated prime word was paired with the same picture. The average length, number of syllables, number of phonemes and frequencies of the names of the target pictures are given, with standard deviations in parentheses. Values were taken from the English Lexicon Project, http://elexicon.wustl.edu/. The pictures were presented in color and were taken from the Hemera Photo Objects database (Hemera Technologies Inc., 2002).
There was no significant difference in log frequency ($F(2, 263) = 0.066$, $p = 0.936$), number of letters ($(2, 263) = 0.886$, $p = 0.414$), number of phonemes ($F(2, 263) = 0.737$, $p = 0.479$), or number of syllables ($F(2, 263) = 1.205$, $p = 0.301$) of the names of target pictures across the three Relationship Types. The pictures were also matched across the three Relationship Types on familiarity (values taken from the MRC Database and available for 73% of the target pictures used), ($F(2, 194) = 1.129$, $p > 0.325$).

framework described above (e.g. Dell and Chang, 2014; Oppenheim et al., 2010), this interference effect is attributed to the costs of inhibiting competing connections (between the prime's semantic features and its lexical form), as the producer strengthens the specific set of connections between the target's semantic features and its lexical form prior to production.[2]

If, in schizophrenia, the automatic spread of activity between related features with semantic memory is intact, the N400 priming effect prior to producing semantically related (versus unrelated) targets should be the same as in healthy controls. Moreover, if, as in healthy controls, people with schizophrenia are able to inhibit competing connections between the prime's semantic features and its lexical form, then they should also show a later behavioral semantic interference effect, with longer naming times to semantically related than unrelated targets.

2. Do automatic semantic disturbances prior to language production in schizophrenia stem from lower-level phonemic abnormalities?

To address this second question, we compared ERPs and naming times to target pictures that were immediately preceded by phonemically related prime words (overlapping in their initial phonemic segment, e.g. < picture of a starfish > preceded by "stomach") with unrelated targets (e.g. < picture of a starfish > preceded by "ball"), see Fig. 1B. In healthy adults, this contrast is not associated with modulation on the N400 or any other ERP component (Blackford et al., 2012). This suggests that phonemic activity does not usually feed forward to influence automatic semantic facilitation prior to production. However, naming times are faster to phonemically related than unrelated targets (Blackford et al., 2012; see also Grainger and Ferrand, 1996; Kinoshita, 2000; Schiller, 2008). This may reflect priming that occurs after the ERP epoch at relatively late stages of production, such as phonological or articulatory encoding.

If semantic abnormalities in schizophrenia arise from an abnormal increase in feedforward activation from the phonemic to the semantic level of representation, then patients might show modulation on the N400 to phonemically related (versus unrelated) targets. If, however, phonemic representations and their interactions with semantic representations are relatively preserved, then, like controls, patients should show no modulation on the N400. They should also show no differences from controls on naming times to phonemically related (versus unrelated) targets.

3. Do automatic semantic disturbances prior to language production in schizophrenia stem from abnormalities at the interface between semantic features and lexical form?

Finally, to directly assess the interface between semantic features and lexical form, we compared ERPs and naming times to target pictures that were immediately preceded by identity related prime words, which overlapped in *both* their semantics and their lexical form with the name of the target picture (e.g. < picture of socks > preceded by "socks") with targets preceded by unrelated primes (e.g. < picture of socks > preceded by "waffle"), see Fig. 1C. In healthy adults, this contrast reveals an even larger priming effect on the N400 than that seen in contrasting semantically related and unrelated targets (Blackford et al., 2012). This is because the prime pre-activates not only the semantic features of the target, but also its lexical form, thereby pre-strengthening precise connections between these two levels of representation. Thus, when healthy participants come to produce the name of the target, it is easier for them to strengthen the same connections between its semantic features and its lexical form: they have, in effect, already used the form of the prime to precisely *predict* the semantic features of the target picture.

If, when processing the prime, people with schizophrenia pre-establish relatively more diffuse and weaker connections between its meaning and form, then when they subsequently come to produce the target word and attempt to establish precise connections between its semantic features and its lexical form, these more diffuse connections might compete. This would lead to an interference effect on the N400, with a larger (more negative) N400 to identity related than unrelated targets. Put another way, a failure of patients to use the form of the prime to precisely predict the semantic features of the target may lead to increased competition at the level of the connections between semantic features and lexical form as patients come to produce the target.

2. Materials and methods

2.1. Design and stimuli

The stimuli were almost identical to those described in detail in our previous study in young healthy adults (Blackford et al., 2012). Briefly, 270 pictures of household items, animals, food items, and other easily

[2] There are, however, alternative accounts of the behavioral picture-word semantic interference effect. Some have argued that competition is an inherent part of lemma selection (e.g. Cutting and Ferreira, 1999; Levelt et al., 1999; Roelofs, 2004; see also Starreveld and La Heij, 1996). Others have argued that interference reflects non-competitive processes that occur at a late stage of response selection (Caramazza and Costa, 2000; Mahon et al., 2007).

recognizable objects, were taken from the Hemera Photo Objects database (Hemera Technologies Inc., 2002). Images were 256 × 256 and all had a white background.

These 270 pictures were divided into three sets. Ninety pictures were paired with a *semantically related* prime word, which shared both semantic associations and semantic features with the picture's name; ninety pictures were paired with a *phonemically related* prime word, which shared the same initial phonological segment but not the same initial syllable as the picture's name; ninety pictures were paired with *identity related* prime words, which corresponded to the picture's name.

Then, for each set of 90 related word-picture pairs, a set of unrelated word-picture pairs was created by pseudorandomly pairing the picture targets with prime words that corresponded to the names of other picture targets. An example of each type of related prime-target pair, and its corresponding unrelated pair, is given in Fig. 1. These related and unrelated word-picture pairs were counterbalanced, across two experimental lists, which were seen by different participants. For example, referring to Fig. 1, the < picture of a pie > might appear with the word "cake" in list 2 (semantically related), but with the word "chalk" in list 1 (unrelated); the < picture of a starfish > might appear with the word "stomach" in list 1 (phonemically related) but with the word "ball" (unrelated) in list 2, and a < picture of socks > might be preceded by the word "socks" in list 1 (identity related) but by the word "waffle" in list 2 (unrelated). This design meant that, for each type of relationship, the same sets of targets were seen in related and unrelated conditions across participants. This was important because it reduced the chances that differences between the related and unrelated targets in their visual complexity, familiarity or frequency would confound the ERP findings.

2.2. ERP experiment

2.2.1. Participants

Twenty-four patients with DSM-IV diagnosed schizophrenia were initially recruited from the Erich Lindemann Mental Health Center, Boston, and sixteen healthy volunteers were initially recruited by advertisement. One patient chose to withdraw from the study and, as noted below, four patients were subsequently excluded because of ERP artifact. This left a total of 19 patients and 16 controls whose ERP data were fully analyzed. Healthy volunteers were screened to exclude the presence of psychiatric disorders and were not taking medication affecting the Central Nervous System.

Seventeen of the included patients were receiving stable doses of antipsychotic medication; two patients were not receiving any antipsychotic medication. Three patients were taking anticholinergic medication. In 16 of the 19 patients, symptomatology was assessed (on the day of ERP testing) using the Scale for the Assessment of Positive Symptoms (SAPS: Andreasen, 1984b),[3] the Scale for the Assessment of Negative Symptoms (SANS: Andreasen, 1984a) and the Positive and Negative Syndrome Scale (PANSS: Kay et al., 1987). In Table 1, we report summary data (summed scores) for the SAPS and SANS.

All participants were right-handed and had normal or corrected-to-normal vision. Participants were excluded if they had a history of neurological injury, head trauma with documented cognitive sequelae, medical disorders that can impair neurocognitive function, or if they met DSM-IV criteria for substance abuse within the previous three months or any had lifetime history of substance dependence. Patients and controls participants were closely matched on gender and race/ethnicity distributions and there was no significant difference between the groups in age ($t(33) = 1.074$, $p = 0.291$). The schizophrenia and control groups also showed no significant difference in parental socioeconomic status ($t(33) = 0.294$, $p = 0.770$), as determined by Hollingshead Index scores (Hollingshead, 1965). Demographic characteristics of all participants and clinical details for the schizophrenia group are given in Table 1. Written informed consent was obtained from all participants following the guidelines of the Massachusetts General Hospital and Tufts Human Subjects Research Committees.

Table 1
Demographic, medication and symptom measures. Means are shown with standard deviations in parentheses.

	Control Group	Schizophrenia Group
Gender (M/F)	12/4	15/4
Race (C/AA/Other)	9/4/3	13/2/4
Age (years)	46.75 (6.9)	44.24 (10.4)
Education (years)	13.31 (1.4)	12.71 (1.7)
Parental SES[a]	3.06 (1.2)	2.94 (1.1)
Premorbid IQ[b]	111.18 (6.2)	94.78 (10.4)
CPZ Equivalents (mg)[c]	N/A	458.5 (293.2)
Duration of illness (years)	N/A	22.07 (9.7)
SAPS[d] total	N/A	18.94 (15.0)
SAPS thought disorder	N/A	5.56 (4.0)
SAPS bizarre behavior	N/A	1.75 (2.2)
SAPS delusions	N/A	6.31 (6.2)
SAPS hallucinations	N/A	5.31 (7.1)
SANS[e] total	N/A	41.4 (19.0)

M: Male; F: Female; C: Caucasian; AA: African American.

[a] Parental socio-economic status (SES) was calculated using the Hollingshead Index (Hollingshead, 1965).

[b] Premorbid IQ was assessed using the North American Adult Reading Test: NAART (Blair and Spreen, 1989).

[c] Chlorpromazine (CPZ) Equivalents were calculated following the International Consensus Study of Antipsychotic Dosing (Gardner et al., 2010).

[d] SAPS: Scale for the Assessment of Positive Symptoms (Andreasen, 1984b). For each symptom, summary scores were derived by summing all SAPS scores within the relevant symptom cluster. SAPS total was calculated by summing all scores of all symptoms.

[e] SANS: Scale for the Assessment of Negative Symptoms (Andreasen, 1984a). SANS total was calculated by summing all scores of all symptoms.

2.2.2. Stimulus presentation and EEG recording

Participants were randomly assigned to one of the two lists used for counterbalancing. In order to ensure fairly high naming accuracy during the ERP experiment itself, and following the usual practice for studies of picture naming, all participants were familiarized with the pictures and their expected names prior to the ERP experiment itself.

During the ERP experiment, participants sat in a comfortable chair in a dimly lit room, approximately 60 in. away from a 19-inch CRT monitor, and away from the experimenter. On each trial, a fixation prompt appeared for 500 ms followed by a forward mask ("#######") for 200 ms, followed by the prime word for 60 ms (in white Arial font against a black background), followed by the target picture,[4] which remained on the screen until it was named (with a soft time limit of approximately 2 s), see Fig. 2. In between each trial, participants saw a sign prompting them to blink, written as "(- -)", to reduce the chances of blink artifact during the trials themselves, and this was followed by a blank screen for 350 ms. Participants were instructed to name the pictures as quickly and accurately as possible. Their responses were recorded with in-house software that began recording as soon as the target picture appeared. Participants were given breaks every 15 trials during which they were told that they could move freely.

Twenty-nine tin electrodes recorded the electroencephalogram (EEG), held in place on the scalp by an elastic cap (Electro-Cap International, Eaton, OH). Electrodes were placed in standard

[3] In one patient, we did not complete the SAPS assessment of thought disorder. In another patient, the SAPS assessment of thought disorder was completed on a later date.

[4] Unlike our previous study carried out in young healthy adults (Blackford et al., 2012), the prime word was not followed by a backward mask before the target picture appeared. This was because participants were over 20 years older than in the previous study. The omission of the backward mask increased the likelihood of seeing a semantic priming effect on the N400 with this very short SOA in this older population.

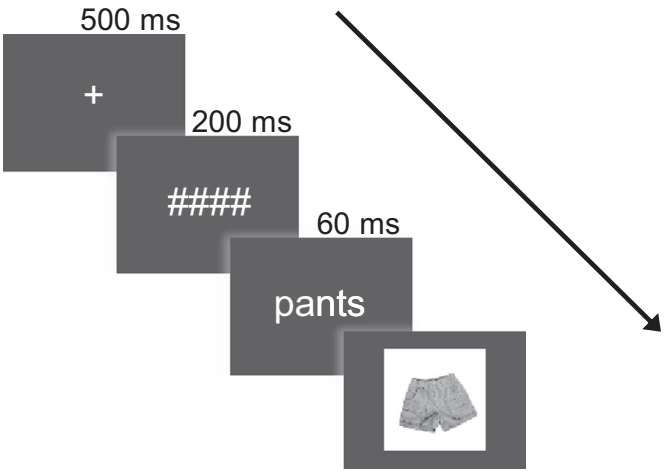

Fig. 2. Trial Presentation. Each trial consisted of a fixation prompt, a forward mask, a briefly-presented content word, and a picture. The picture stayed on the screen until participants named the item (with a soft limit of approximately 2 s).

International 10–20 System locations as well as at 10 additional sites situated primarily between frontal and central sites and between central and parietal sites. Electrodes were also placed below the left eye and at the outer canthus of the right eye to monitor vertical and horizontal eye movements. The EEG signal was amplified by an Isolated Bioelectric Amplifier System Model H&W-32/BA (SA Instrumentation, San Diego, CA) with a bandpass of 0.01–40 Hz and was continuously sampled at 200 Hz by an analogue-to-digital converter.

2.2.3. Behavioral data analysis

For the analysis of accuracy, accurate and inaccurate responses were considered binary outcomes. For the analysis of naming times, we examined accurate trials after first removing outliers (responses exceeding two standard deviations above the mean of that participant's mean naming time across all conditions) and then logarithmically transforming the data to reduce skew.

Both these accuracy and naming time data were analyzed with linear mixed-effect regression models over single-trial data. These models were fit in R version 3.2.4 (R Core Team, 2016) using the "lme4" package version 1.1-11 (see Bates et al., 2015). For the accuracy model, we used logistic regression (appropriate for binary outcome responses).

As described in the Materials and methods, the same target pictures were counterbalanced across related and unrelated conditions for each type of Relationship (see Fig. 1). This resulted in a design in which prime-target Relatedness (related vs. unrelated) was nested within Relationship Type (semantic, phonemic, identity). Thus, in both the accuracy and naming time models, Relationship Type and Relatedness were within-participant fixed factors and Group (control, schizophrenia) was a between-participant fixed factor. The maximal identifiable random-effects structure was used (Barr et al., 2013): by-item and by-subject random intercepts, and by-item and by-subject random slopes for Relatedness and Relationship Type.

The significance of all main effects and interactions involving any of the fixed factors (Group, Relatedness, and Relationship Type) was assessed using type-III sum of squares estimates. In the accuracy model, *p* values were estimated using a Wald approximation, as implemented by the "car" package version 2.1–3 (Fox and Weisberg, 2011). In the naming time model, p values were estimated using a Satterthwaite approximation, as implemented by the "lmerTest" package version 2.0–30 (Kuznetsova et al., 2015).

In both accuracy and naming time models, any interactions involving Relatedness were followed up with the fitted coefficients or, in post hoc models, within each level of Group or Relationship Type (as appropriate) with coefficient *p*-values estimated using Satterthwaite approximations.

2.2.4. ERP data analysis

ERPs were averaged off-line at each electrode site in each experimental condition. We elected a priori to use a − 50 to + 50 ms baseline for analyses, following our previous study using the same paradigm in young healthy participants (Blackford et al., 2012).[5]

ERPs were averaged across all trials, which had the advantage of maximizing power and maintaining counterbalancing across lists. Across all participants, the lowest value in the range of mean naming times was 761 ms, and so, to avoid speech-related artifact, we only analyzed and show ERP activity up until 650 ms post-picture onset (in some participants, there were some individual trials with naming times of < 650 ms but these constituted < 3% of all trials across all participants). Trials contaminated with eye artifact (detected using a polarity inversion test on the left eye channel) or amplifier blockage were excluded from analyses. As noted above, four patients were excluded altogether from the ERP analysis because of high artifact rejection rates (> 50% of trials excluded). Across the remainder of the participants, artifact contamination from eye movement or amplifier blocking led to the rejection of 17% of trials in patients and 13% in controls. This did not differ between the two groups (all Fs < 1.849, *ps* > 0.171), but it did differ between the three Relationship Types ($F(2,66) = 7.572$, $p < 0.005$), due to more rejections in the identity related and corresponding unrelated trials, than in either the phonemically related and unrelated trials ($t(34) = 2.606$, $p < 0.05$) or the semantically related and unrelated trials ($t(34) = 4.065$, $p < 0.001$). There was no Relatedness by Relationship Type interaction ($F(2,66) = 0.973$, $p = 0.372$).

ERP data from a representative sub-array of nine channels were used for analysis. This sub-array constituted three columns over the left, center, and right hemisphere, each with three electrode sites extending from the front to the back of the head (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4). This allowed us to use the same analysis strategy that we used in our previous study using the same paradigm in young healthy individuals (Blackford et al., 2012). Also following this previous study, we examined three ERP components: the N/P150 between 100-200ms, the N250/N300 between 200-350 ms (Eddy & Holcomb, 2010), and the N400 between 350-550 ms. We also followed another previous ERP study examining automatic semantic priming in people with schizophrenia (Kreher et al., 2008) by further subdividing the N400 component into two 100 ms epochs to give a finer-grained assessment within this time window. However, given that this subdivision of the N400 increased the probability of Type 1 error (see Luck and Gaspelin, 2017 for recent discussion), for any analysis that yielded a significant difference between the schizophrenia and control groups in N400 modulation (at an alpha of $p \leq 0.05$), we carried out a supplementary mass univariate analysis to determine whether the effect remained significant at all sampling points within the 350-550 ms time at 17 contiguous electrode sites (F3, Fz, F4, FC5, FC1, FC2, FC6, C3, Cz, C4, CP5, CP1, CP2, CP6, P3, Pz, P4), using a cluster-based permutation test to account for multiple comparisons (Maris and Oostenveld, 2007; Groppe et al., 2011). This approach explicitly accounts for multiple comparisons while retaining the ability to localize ERP effects on the scalp surface (Luck, 2014). Indeed, recent simulations in our lab show that, for relatively widespread effects, when used in combination with a cluster mass test, it does not sacrifice power to detect ERP effects

[5] In Blackford et al., 2012, we used a − 50 to + 50 ms baseline because the use of a − 100–0 ms pre-stimulus baseline revealed some divergence across some conditions at time-point zero — not an uncommon problem with masked priming studies in which events unfold in very fast succession just prior to the onset of a target. In the present study, we repeated all analyses that showed significant differences in N400 modulation between patients and controls using a − 100–0 ms pre-stimulus baseline. The pattern of findings was the same.

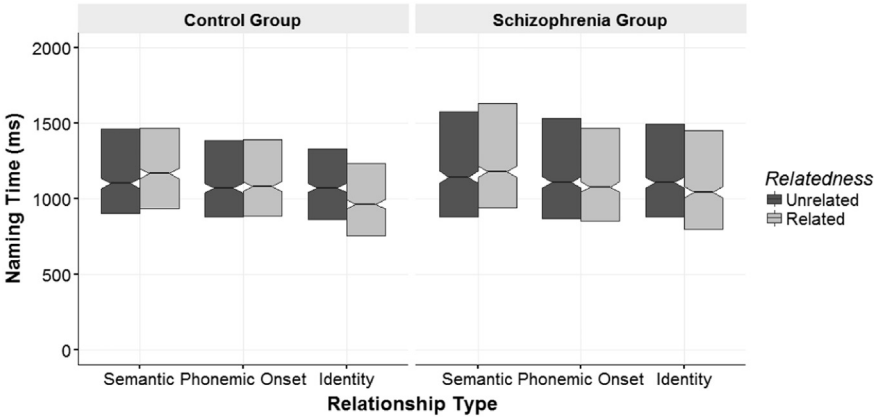

Fig. 3. Naming times in the control and schizophrenia groups. Naming times were calculated as the time from the onset of correctly-named target pictures until the onset of the verbal response (excluding disfluencies like "um"). Black horizontal lines in each box indicate the median naming time across all trials of that condition from all participants in each participant group, with a notch indicating a 95% confidence interval for the median. The top and bottom box boundaries indicate the 3rd and 1st quartiles, respectively.

(Fields, 2017). Details of these methods and results are reported in Supplementary Materials.

For each time window, we started with an omnibus ANOVA to determine whether, within that time window, the semantic relatedness effect, the phonemic relatedness effect and the identity relatedness effect differed between the control and schizophrenia groups. As noted above and in the Methods, for each of these three types of relationship, the same 90 targets were paired with 90 unrelated prime words (counterbalanced across lists). Thus, in these omnibus ANOVAs, Relatedness (related, unrelated) was nested within Relationship Type (identity, semantic, phonemic), and both were included as within-subject factors. Group (control, schizophrenia) was a between-participant factor. These omnibus models also included Laterality (left, midline, right), and Anterior Posterior (AP) Distribution electrode placement (frontal, central, parietal) as within-subject factors.

Any interactions that involved Group, Relatedness and Relationship Type were then followed up with planned ANOVAs to examine effects of Relatedness for each Relationship Type. In these ANOVAs, the within-subject factors were Relatedness (semantically related versus unrelated; phonemically related versus unrelated; identity related versus unrelated) as well as Laterality and AP Distribution. Again, the between-subject factor was Group. Interactions involving Group were further followed up by examining effects of Relatedness in the control and schizophrenia groups separately. In reporting results, we use the Greenhouse-Geisser correction (Greenhouse and Geisser, 1959).

2.2.5. Relationships between ERP effects and clinical measures within the schizophrenia group

We carried out planned correlations within the schizophrenia group to examine the relationships between thought disorder, as assessed using the SAPS (summed score), and modulation of the N400. The N400 effects were captured by subtracting activity to the semantically related or identity related targets from their corresponding unrelated targets, each averaged across a three-electrode central region (C3, Cz, C4) within the late N400 time window (450-550 ms). We examined Spearman's correlations. Alpha was set at 0.05, although we note that, given the small sample size, results significant at this level should be considered preliminary.

We also carried out exploratory post hoc analyses examining relationships between these N400 effects and SAPS scores of delusions, hallucinations and bizarre behavior (each assessed by summing all SAPS scores within the relevant symptom cluster), as well as total positive symptoms (summed across all SAPS items), total negative symptoms (summed across all SANS items), and medication dosage (in chlorpromazine equivalents, calculated following Gardner et al., 2010). Results of these exploratory analyses are reported in Supplementary Materials.

3. Results

3.1. Behavioral results

One control's behavioral data was missing because of equipment failure, and was therefore excluded from the behavioral analyses.

3.1.1. Accuracy

The differences in overall accuracy between the control group (mean: 92.3%, SD: 26.6%) and the schizophrenia group (mean: 90.2%, SD 29.7%) did not reach significance (main effect of Group, χ^2 (1) = 3.33, p = 0.068). There was also no significant difference between the two groups in the effects of Relatedness or Relationship Type (no interactions between either Group and Relatedness, χ^2 (1) = 1.70, p = 0.192, or between Group and Relationship Type, χ^2 (2) = 0.11, p = 0.945, or between all three factors, χ^2 (2) = 5.55, p = 0.062).

Across the two groups, there was a main effect of Relatedness, which reflected more accurate naming of related than unrelated targets (χ^2 (1) = 22.58, p < 0.001). In addition, there was a significant interaction between Relationship Type and Relatedness (χ^2 (2) = 7.72, p = 0.021). This interaction resulted from (a) a significant difference between the effect of Relatedness in comparing the identity related (versus unrelated) trials, and the semantically related (versus unrelated) trials (z = 2.12, p = 0.034), as well as (b) a significant difference between the effect of Relatedness in comparing the identity related (versus unrelated) trials and the phonemically related (versus unrelated) trials (z = 2.63, p = 0.009). Follow-ups revealed no significant differences in errors between naming identity related and unrelated pictures (β = 0.127, z = 0.37, p = 0.71), but more errors in naming semantically related than unrelated pictures (β = 0.848, z = 4.10, p < 0.001), and more errors in naming phonemically related pictures than unrelated pictures (β = 0.702, z = 2.18, p = 0.029).

3.1.2. Naming times

Participants' naming times for each correctly-named target picture in each condition are shown in the boxplot in Fig. 3. There were no overall differences in naming times between the schizophrenia and control groups (no main effects of Group: F(1, 30.4) = 0.36, p = 0.554), and no difference between the two groups in the pattern of naming times across conditions (no interactions involving Group, ps > 0.18). Across both groups, related items were named significantly faster than unrelated items (main effect of Relatedness: F(1, 36.8) = 5.16, p = 0.029). In addition, across both groups, the effect of Relatedness on naming times differed between the three Relationship Types (interactions between Relatedness and Relationship Type, F(2, 248.6) = 16.30, p < 0.001). This was due to a significant difference in the effect of Relatedness in comparing the identity related (versus unrelated) trials, and the semantically related (versus unrelated) trials (interaction t = 4.35, p < 0.001): whereas identity related pictures

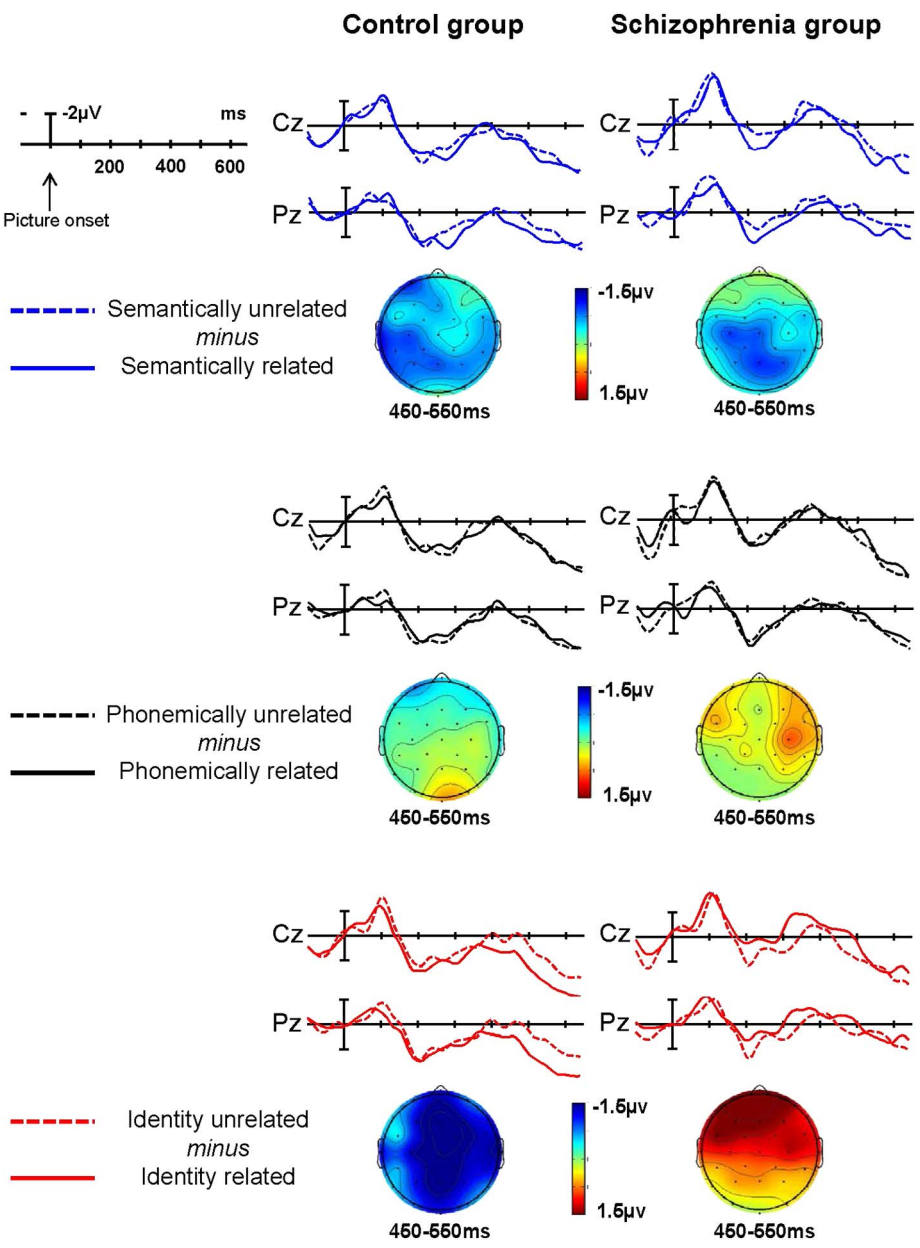

Fig. 4. Grand-averaged waveforms in the control and schizophrenia groups. Negative voltage is plotted upwards. Waveforms (shown at Cz and Pz) evoked by target pictures that were preceded by prime words that were related to the target's name along three dimensions are shown as solid lines: Semantic (blue), Phonemic (black) and Identity (red). For each of these three relationship types, waveforms produced by the same targets when preceded by unrelated primes are shown as dotted lines. Voltage maps show differences between ERPs evoked by each of these contrasts in the late N400 time window (450–550 ms). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

were named significantly faster than unrelated pictures ($\beta = -0.031$, $t = -3.27$, $p = 0.002$), semantically related pictures were named significantly *slower* than unrelated pictures ($\beta = 0.014$, $t = 2.12$, $p = 0.037$). There was no significant difference in the effect of Relatedness the identity related (versus unrelated) trials, and the phonemically related (versus unrelated) trials (interaction $t = 1.37$, $p = 0.17$): in both cases, naming times were faster to related than to unrelated targets.

3.2. ERP results

Grand average ERPs, time-locked to the presentation of target pictures, together with voltage maps in the late N400 time window are plotted in Fig. 4.

3.2.1. 100–200 ms: N/P150

There were no main effects or interactions involving Relatedness in this time window (all Fs < 3.054, all *ps* > 0.057).

3.2.2. 200–350 ms: N250/N300

The omnibus ANOVA revealed an interaction between Group, Relatedness, and Relationship Type ($F(2,66) = 3.497$, $p < 0.05$), as well as between Group, Relatedness, and AP Distribution ($F(2,66) = 3.818$, $p < 0.05$).

Comparisons between the semantically related and unrelated targets and between the phonemically related and unrelated targets revealed no significant effects involving Group and/or Relatedness (all Fs < 2.175, all *ps* > 0.136). However, in comparing the identity related and unrelated targets, there were interactions between Relatedness and Group ($F(1,33) = 7.451$, $p < 0.05$), as well as between Relatedness, Group and AP Distribution ($F(2,66) = 3.996$, $p < 0.05$). These interactions arose because the schizophrenia group produced a larger N250/N300 prior to naming identity related than unrelated pictures ($F(1,18) = 6.777$, $p < 0.05$), but there was no effect of Relatedness in the control group within this time window ($F(1,15) = 1.493$, $p < 0.241$).

3.2.3. The N400: 350–450 ms and 450–550 ms

The omnibus ANOVA revealed an interaction between Relatedness,

Relationship Type and Laterality ($F(4132) = 3.084$, $p < 0.05$) in the early N400 time window, and between Group and Relatedness ($F(1,33) = 5.065$, $p < 0.05$), Group, Relatedness and AP Distribution ($F(2,66) = 3.644$, $p < 0.05$), and Group, Relatedness and Relationship Type ($F(2,66) = 5.087$, $p < 0.01$) in the late N400 time window.

The pair-wise ANOVAs contrasting the semantically related and unrelated targets showed no interactions involving Group and Relatedness (all $Fs < 1.851$, $ps > 0.169$). However, across all participants, there were interactions between Relatedness and AP Distribution (approaching significance in the early N400 time window, $F(2,66) = 2.748$, $p = 0.086$, and significant in the late N400 time window, $F(2,66) = 3.705$, $p < 0.05$), reflecting an N400 semantic priming effect that was maximal at central and parietal sites in the late time window (C3, P3, Pz, P4, all $ps < 0.05$), see Fig. 4, top.

In comparing the phonemically related and unrelated targets, there were no significant interactions with Group, and no effects involving Relatedness in either the early or late N400 time window (all $Fs < 2.977$, all $ps > 0.067$), see Fig. 4, middle.

The pair-wise ANOVAs contrasting the identity related and unrelated targets revealed interactions between Group and Relatedness in both the early and late N400 time windows (early N400 time window: $F(1,33) = 5.156$, $p < 0.05$; late N400 time window, $F(1,33) = 14.073$, $p < 0.01$). This interaction appeared to be driven by an N400 priming effect in controls (a smaller/less negative-going N400 to identity related than to unrelated targets) but a reverse N400 effect in patients (a larger/more negative-going N400 to the identity related than the unrelated targets), see Fig. 4, bottom. In the early N400 time window, these within-subject comparisons approached significance (controls: $F(1,18) = 2.186$, $p < 0.15$; patients: $F(1,15) = 3.065$, $p < 0.10$), and in the late N400 time window, both the priming effect in controls and the reverse effect in patients were significant (controls: $F(1,15) = 9.822$, $p < 0.01$; patients: $F(1,18) = 4.829$, $p < 0.05$). A mass univariate analysis that examined all sampling points across the 350-550 ms time window at 17 electrode sites (F3, Fz, F4, FC5, FC1, FC2, FC6, C3, Cz, C4, CP5, CP1, CP2, CP6, P3, Pz, P4), with a cluster-based permutation test to account for multiple comparisons (Maris and Oostenveld, 2007; Groppe et al., 2011), revealed the same pattern of findings (see Supplementary Materials for full report).

3.2.4. Clinical characteristics

We found an inverse correlation between SAPS thought disorder scores (summed) and the magnitude of the semantic priming effect within the late N400 time window (450-550 ms), Spearman's $r = 0.5$, $p = 0.05$: patients with more severe thought disorder showed a smaller N400 semantic priming effect. There was no correlation between thought disorder and the magnitude of the identity priming N400 effect ($ps > 0.9$). Because of the relatively small number of patients and limited range of thought disorder, we consider these findings preliminary. We report additional exploratory post hoc correlations between N400 effects and clinical measures within the schizophrenia group in Supplementary Materials.

4. Discussion

In this study, we show an abnormal pattern of neural activity associated with automatic semantic processing before word production in schizophrenia. By time-locking ERPs to the onset of target pictures and measuring the N400, we were able to index automatic semantic activity associated with retrieving the target picture's name before production (see Blackford et al., 2012). Abnormalities in semantic activity in schizophrenia, however, were not seen in all situations. When people with schizophrenia named targets that shared only the semantic properties of their prime words then, just as in controls, the N400 was smaller (less negative) than when they named targets preceded by unrelated prime words — a normal automatic N400 semantic priming effect. Abnormalities were only observed when people with schizophrenia named targets that shared both the semantic properties and the lexical form of their preceding prime words: the amplitude of the N400 evoked by these identity related targets was larger (more negative) than the N400 evoked by unrelated targets — a *reversal* of the normal N400 identity priming effect. As discussed below, we suggest that this reversed pattern of N400 modulation in schizophrenia resulted from increased competition at the level of adapting connections between the target's semantic features and its lexical form prior to production. We now return to the three questions posed in the Introduction before discussing the more general implications of our findings.

1. Do automatic semantic disturbances prior to language production in schizophrenia stem from a primary disturbance in semantic memory?

The degree of attenuation of the N400 to target pictures preceded by semantically related versus unrelated primes was the same in people with schizophrenia as in healthy controls. This suggests that there was no primary disturbance in the spread of automatic activity across directly related concepts within semantic memory. In both groups, the prime automatically pre-activated the semantic features of the target with the same strength, making it easier for participants to access these semantic features and begin to map them on to the lexical form of the target, prior to its production, see Fig. 5A&B, panels 1 and 2. This is consistent with previous studies of automatic direct semantic priming that have used recognition tasks (e.g.Barch et al., 1996; Blum and Freides, 1995; Chapin et al., 1992; Ober et al., 1995; Vinogradov et al., 1992).

In addition, like healthy controls, people with schizophrenia were *slower* to name targets that were preceded by semantically related versus unrelated prime words — the picture-word semantic interference effect (Alario et al., 2000; Lupker, 1979; Rosinski, 1977). In both groups, we attribute this behavioral interference effect to processes that occurred at a later stage of processing, following the N400 time window (see Blackford et al., 2012). More specifically, we suggest that it reflected costs of inhibiting connections between semantic features that were shared between the prime and target, and the prime's lexical form (competitive inhibition, cf. Oppenheim et al., 2010), with these costs being incurred only after lexical selection was complete, see Fig. 5A&B, panel 3; (for alternative explanations of the picture-word semantic interference effect see footnote 2 and Blackford et al., 2012).

2. Do automatic semantic disturbances prior to language production in schizophrenia stem from lower-level phonemic abnormalities?

Again, our findings provide no support for this hypothesis: we saw no differences between the two groups in the pattern of ERPs or naming times to target pictures that were preceded by phonemically related (versus unrelated) prime words. The absence of any modulation on the N400 in people with schizophrenia suggests that, as in healthy controls, any pre-activation of the phonemic representations by the prime did not influence semantic processing of the target within the N400 time window.

3. Do automatic semantic disturbances prior to language production in schizophrenia stem from abnormalities of the connections between semantic features and lexical form?

Our ERP findings are consistent with this third hypothesis: people with schizophrenia and healthy controls showed clear differences in how the N400 was modulated prior to naming target pictures that were preceded by identity related primes (overlapping with the names of these targets in *both* their semantic features and in their lexical form), relative to target pictures that were preceded by unrelated primes.

Under these conditions, controls showed the expected identity priming effect on the N400, with a smaller amplitude N400 to identity

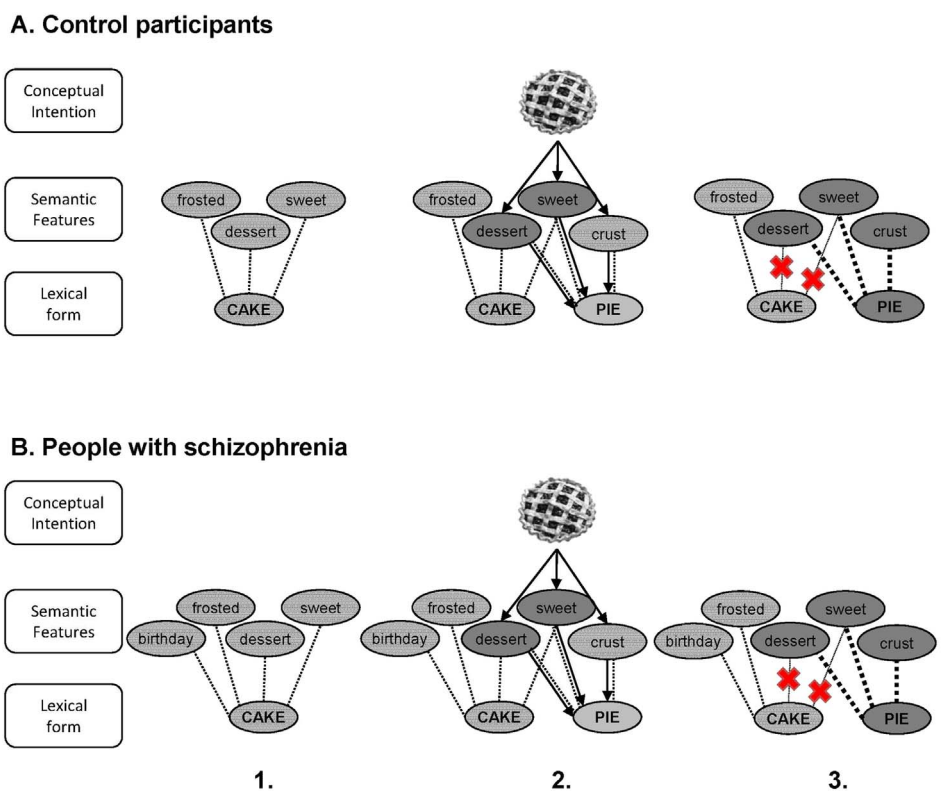

Fig. 5. Diagrammatic depiction of proposed processing and adaptation/learning mechanisms engaged when (A) healthy control participants and (B) people with schizophrenia name target pictures that are immediately preceded by masked semantically related prime words. Dotted lines are used to indicate connections across semantic and lexical form levels of representation, with the thickness of the lines depicting the strength of connections. Arrows are used to indicate the flow of activity prior to production.
1. The connections established between the lexical form of the masked prime and its semantic features (dotted lines) are weaker and more diffuse in people with schizophrenia than in healthy control participants.
2. As participants prepare to name the target picture, they retrieve its semantic features and map them on to the target's lexical representation. In both control and patient groups, a subset of these semantic features have been pre-activated by the semantically related prime (dark gray), and so this mapping process is facilitated. Thus, the amplitude of the N400 evoked by semantically related (versus unrelated) targets is reduced in both the control and patient groups.
3. Learning/adaptation is initiated when the selection of the target's lexical form is complete. This entails strengthening the connections between the target's lexical form and its semantic features (indicated using dark dotted lines) and diminishing the strength of any competing connections between the subset of semantic features shared by the prime, and the prime's lexical form (indicated with light dotted lines and crosses). In both control and patient groups, this competitive learning process leads to longer naming times to semantically related than unrelated targets: the behavioral semantic interference effect.

related than to unrelated targets. This facilitation effect is thought to arise because the prime pre-activated both the semantic features and the lexical form of the target, pre-strengthening strong and precise connections between these levels of representation (see Fig. 6A, panels 1 and 2). Patients, however, showed a reversed effect, with a larger amplitude N400 to identity related than to unrelated targets. Given that, as discussed above, semantic and phonemic processing were preserved in the same patients, we interpret this interference effect on the N400 as reflecting disruption at the level of adapting connections between semantic features and lexical form within the N400 time window (cf. Oppenheim et al., 2010). More specifically, we suggest that when processing the prime, patients established weaker and less precise connections than controls (see Fig. 6B, panel 1). These more diffuse connections competed when patients came to strengthen the connections between the target's semantic features and its form prior to production (see Fig. 6B, panel 2). This interference occurred within the N400 time window because the prime had already pre-activated the target's lexical form by the time processing of the target began. We suggest that these costs outweighed any effects of semantic facilitation by the prime, leading to the reversal of the N400 effect.

Despite this interference effect on the N400, people with schizophrenia, like healthy controls, did show a facilitatory effect on naming times to identity related (versus unrelated) targets. In controls, this behavioral facilitation is thought to result primarily from facilitated encoding of phonological representations at a later stage of processing that follows the N400 time window (see Blackford et al., 2012). The preserved behavioral facilitation in patients therefore suggests that phonological encoding itself was intact in schizophrenia.

4.1. Theoretical implications

We have interpreted the present set of findings within a connectionist framework, which posits close links between language comprehension, production and adaptation (e.g. Oppenheim et al., 2010; Dell and Chang, 2014). They can also be understood in relation to other theoretical frameworks that posit these types of links. For example, within a probabilistic generative framework, both language comprehension and production entail the continual generation of implicit probabilistic predictions in an ongoing attempt to refine our internal (generative) model of the statistical structure of our external environment. Any differences between our predictions and actual inputs — prediction error — lead us to dynamically adapt (update) the statistical contingencies that comprise the structure of this internal model so that we are able to predict more accurately in the future (e.g. Brown and Kuperberg, 2015; Jaeger and Snider, 2013; Kleinschmidt and Jaeger, 2015).[6] In the present paradigm, healthy controls used the lexical form of the prime to precisely predict the semantic features of the target. Thus, when they came to retrieve these semantic features in order to produce the name of the target picture, there was no semantic prediction error and a small amplitude N400 was produced. In contrast, we suggest that because people with schizophrenia failed to use the prime to precisely predict the semantic features of the target, this led to an abnormally large semantic prediction error. This, in turn led to increased costs of adjusting statistical contingencies between the target's semantic features and its lexical form prior to production and to a larger amplitude N400.[7] This interpretation is in keeping with the more general proposal that a breakdown of probabilistic prediction and updating mechanisms can explain multiple symptoms (Fletcher and Frith,

[6] Within a probabilistic generative framework, adaptation entails updating beliefs about statistical contingencies across levels of representation (distributional learning). This contrasts with a connectionist framework in which adaptation/learning is conceptualized as entailing an adjustment of connection weights across levels of representation. For more general discussions of this type of framework, see Clark (2013), Friston (2010), and Jacobs and Kruschke (2011).

[7] While in the present paradigm, predictions were based on bottom-up input from the lexical form of the prime, it is also possible that such unconstrained prediction error and inappropriate adaptation prior to production in schizophrenia results from a failure of patients to predict their own speech plans with the same precision as healthy controls (see Adams et al., 2013 for discussion).

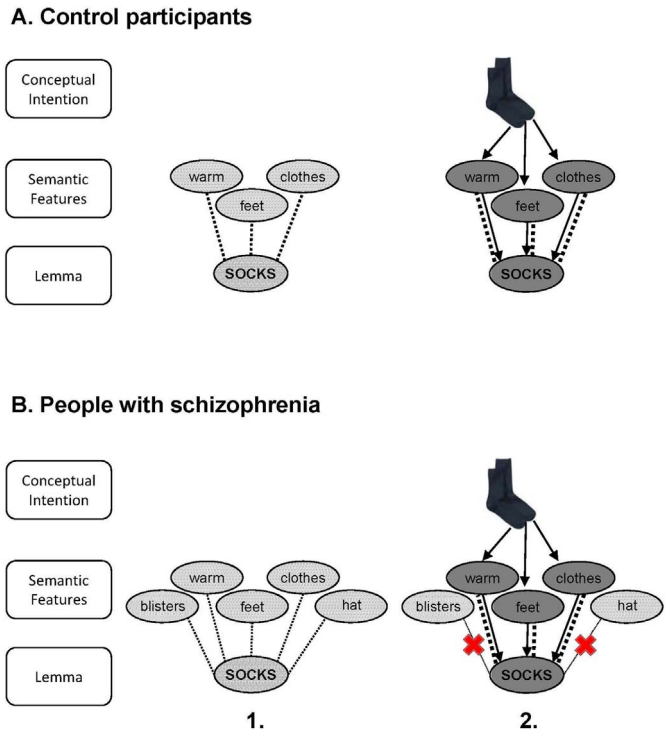

Fig. 6. Diagrammatic depiction of processing and learning mechanisms engaged when (A) healthy control participants and (B) people with schizophrenia name target pictures that are immediately preceded by masked identity related prime words. Dotted lines are used to indicate connections across levels of representation, with the thickness of the lines depicting the strength of connections. Arrows are used to indicate the flow of activity prior to production.

1. The connections established between the lexical form of the masked prime and its semantic features (dotted lines) are weaker and more diffuse in people with schizophrenia than in healthy control participants.

2. As participants prepare to name the target picture, they retrieve its semantic features and map them on to the target's lexical form. Learning/adaptation is initiated when selection of the target's lexical form is complete (this occurs earlier than for semantically related targets because the target's lexical form was pre-activated by the identity related prime). In control participants, this whole process is facilitated in comparison with preparing to name unrelated targets, leading to a smaller N400 amplitude to identity related than unrelated targets. In people with schizophrenia, however, learning/adaptation entails strengthening the connections between the target's lexical form and its semantic features (indicated using dark dotted lines) and diminishing the strength of any competing connections (indicated with light dotted lines and crosses). This competitive learning process leads to a larger N400 amplitude to identity related than to unrelated targets: a reversed N400 effect.

2009; Corlett et al., 2010), as well as multiple abnormalities in both language comprehension and production (Brown and Kuperberg, 2015) in schizophrenia.

4.2. Open questions

Our findings leave open a number of questions. First, are abnormalities associated with language production in schizophrenia constrained to the connections between meaning and lexical form, or do they also impact connections between lower levels of representation (e.g. between phonemic and articulatory representations), which would impact later stages of production? Although our behavioral data suggest that these later stages of processing were relatively preserved in schizophrenia, we only analyzed ERPs that were time-locked to the onset of the target stimulus. This is appropriate for examining the N400, which has a stable latency (Federmeier and Laszlo, 2009) and which, as noted above, is thought to capture the process of mapping the target's semantic features on to its lexical form prior to production (see Blackford et al., 2012, pages 96–97). Later stages of production, however, may be more likely to vary across trials and across individuals, and may therefore be better indexed by time-locking to participants' articulatory responses, and examining ERPs prior to this point. Examining such response-locked ERPs carries more risk of articulatory artifact (see Porcaro et al., 2015 for a recent discussion), and also introduces challenges of identifying the precise onset of articulation (see Fargier et al., 2017). However, this approach does have some precedent in schizophrenia research (see Ford et al., 2007), and it may be possible to modify the paradigm used in the present study to address this question.

Second, how are the abnormalities identified here linked to the clinical phenomenon of thought disorder in schizophrenia? In present study, the interference effect on the N400 observed prior to word production was detected in the schizophrenia group as a whole. This included patients without significant thought disorder. And, indeed, for the most part, these patients successfully produced the words they intended, as evidenced by their preserved pattern of accuracy and naming times. One possibility is that thought disorder reflects an extreme manifestation of the underlying disturbances described here. On this account, in some patients, over time, a failure to maintain finely-tuned connections between form and meaning results in an indiscriminate and broader automatic spread of semantic activity (see Brown and Kuperberg, 2015). This, in turn, would lead to increased difficulty in selecting the correct lexical form, and ultimately to the intrusion of associated items into speech — the clinical phenomenon that characterizes positive thought disorder. In the present paradigm, some preliminary evidence for this idea comes from our observation that patients with more thought disorder showed a smaller semantic N400 et al., 1992; Ober et al., 1995; Vinogradov et al., 1992). effect (although we note that similar inverse correlations were also seen with delusions and bizarre behavior, see Supplementary Material). This may be because, in more thought-disordered patients, an indiscriminate automatic spread of semantic activity from the prime interfered with the retrieval of the target's semantic features within the N400 time window, reducing any effect of semantic facilitation within this time window.

5. Conclusion

In sum, we have shown that schizophrenia is associated with abnormal automatic semantic activity just a few hundred milliseconds prior to word production. We further localized this abnormality to the interface between semantic features and lexical form. We suggest that this abnormality stems from impairments of fast adaptation, resulting from a breakdown of predictive and updating mechanisms, which have been previously discussed in relation to other aspects of language processing and multiple symptoms and cognitive disturbances in schizophrenia.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2017.12.026.

References

Adams, R.A., Shipp, S., Friston, K.J., 2013. Predictions not commands: active inference in the motor system. Brain Struct. Funct. 218, 611–643.

Alario, F.X., Segui, J., Ferrand, L., 2000. Semantic and associative priming in picture naming. Q. J. Exp. Psychol. A Hum. Exp. Psychol. 53, 741–764.
Andreasen, N.C., 1984a. Scale for the Assessment of Negative Symptoms (SANS). The University of Iowa, Iowa City.
Andreasen, N.C., 1984b. Scale for the Assessment of Positive Symptoms (SAPS). The University of Iowa, Iowa City, IA.
Andreasen, N.C., Grove, W.M., 1986. Thought, language, and communication in schizophrenia: diagnosis and prognosis. Schizophr. Bull. 12, 348–359.
Barch, D.M., Cohen, J.D., Servan-Schreiber, D., Steingard, S., Steinhauer, S., van Kammen, D., 1996. Semantic priming in schizophrenia: an examination of spreading activation using word pronunciation and multiple SOAs. J. Abnorm. Psychol. 105, 592–601.
Barr, D.J., Levy, R., Scheepers, C., Tily, H.J., 2013. Random effects structure for confirmatory hypothesis testing: keep it maximal. J. Mem. Lang. 68, 255–278.
Bates, D.M., Mächler, M., Bolker, B., Walker, S., 2015. Fitting linear mixed-effects models using lme4. J. Stat. Softw. 67, 1–48.
Blackford, T., Holcomb, P.J., Grainger, J., Kuperberg, G.R., 2012. A funny thing happened on the way to articulation: N400 attenuation despite behavioral interference in picture naming. Cognition 123, 84–99.
Blair, J.R., Spreen, O., 1989. Predicting premorbid IQ: a revision of the National Adult Reading Test. Clin. Neuropsychol. 3, 129–136.
Bleuler, E., 1911/1950. Dementia Praecox, or the Group of Schizophrenias. International Universities Press, New York.
Blum, N.A., Freides, D., 1995. Investigating thought disorder in schizophrenia with the lexical decision task. Schizophr. Res. 16, 217–224.
Brown, M., Kuperberg, G.R., 2015. A hierarchical generative framework of language processing: linking language perception, interpretation, and production abnormalities in schizophrenia. Front. Hum. Neurosci. 9, 643.
Caramazza, A., 1997. How many levels of processing are there in lexical access? Cogn. Neuropsychol. 14, 177–208.
Caramazza, A., Costa, A., 2000. The semantic interference effect in the picture-word interference paradigm: does the response set matter? Cognition 75, B51–64.
Chapin, K., McCown, J., Vann, L., Kenney, D., Youssef, I., 1992. Activation and facilitation in the lexicon of schizophrenics. Schizophr. Res. 6, 251–255.
Chauncey, K., Holcomb, P., Grainger, J., 2009. Primed picture naming within and across languages: an ERP investigation. Cogn. Affect. Behav. Neurosci. 9, 286–303.
Clark, A., 2013. Whatever next? Predictive brains, situated agents, and the future of cognitive science. Behav. Brain Sci. 36, 181–204.
Corlett, P.R., Taylor, J.R., Wang, X.J., Fletcher, P.C., Krystal, J.H., 2010. Toward a neurobiology of delusions. Prog. Neurobiol. 92, 345–369.
Cutting, J., Ferreira, V., 1999. Semantic and phonological information flow in the production lexicon. J. Exp. Psychol. Learn. Mem. Cogn. 25, 318–344.
Dell, G.S., Chang, F., 2014. The P-chain: relating sentence production and its disorders to comprehension and acquisition. Philos. Trans. R. Soc., B 369, 20120394.
Dell, G.S., Chang, F., Griffin, Z.M., 1999. Connectionist models of language production: lexical access and grammatical encoding. Cogn. Sci. 23, 517–542.
Eddy, M., Holcomb, P., 2010. The temporal dynamics of masked repetition picture priming effects: manipulations of stimulus-onset asynchrony (SOA) and prime duration. Brain Res. 1340, 24–39.
Elvevåg, B., Foltz, P.W., Weinberger, D.R., Goldberg, T.E., 2007. Quantifying incoherence in speech: an automated methodology and novel application to schizophrenia. Schizophr. Res. 93, 304–316.
Fargier, R., Bürki, A., Pinet, S., Alario, F., Laganaro, M., 2017. Word Onset Phonetic Properties and Motor Artifacts in Speech Production EEG Recordings. Psychophysiology.
Federmeier, K., Laszlo, S., 2009. Time for meaning: electrophysiology provides insights into the dynamics of representation and processing in semantic memory. Psychol. Learn. Motiv. 51, 1–44.
Fields, E.C., 2017. Chapter 3: The Problem of Evidentiary Value in the Statistical Analysis of ERP Data and Mass Univariate Statistics As a Solution. Dissertation: "Event-related potential and functional MRI studies of emotion and self-relevance.". Tufts University.
Fletcher, P.C., Frith, C.D., 2009. Perceiving is believing: a Bayesian approach to explaining the positive symptoms of schizophrenia. Nat. Rev. Neurosci. 10, 48–58.
Ford, J.M., Roach, B.J., Faustman, W.O., Mathalon, D.H., 2007. Synch before you speak: auditory hallucinations in schizophrenia. Am. J. Psychiatr. 164, 458–466.
Fox, J., Weisberg, S., 2011. An {R} Companion to Applied Regression, 2nd ed. Sage, Thousand Oaks, CA.
Friston, K.J., 2010. The free-energy principle: a unified brain theory? Nat. Rev. Neurosci. 11, 127–138.
Gardner, D.M., Murphy, A.L., O'Donnell, H., Centorrino, F., Baldessarini, R.J., 2010. International consensus study of antipsychotic dosing. Am. J. Psychiatr. 167, 686–693.
Grainger, J., Ferrand, L., 1996. Masked orthographic and phonological priming in visual word recognition and naming: cross-task comparisons. J. Mem. Lang. 35, 623–647.
Grainger, J., Holcomb, P.J., 2009. Watching the word go by: on the time-course of component processes in visual word recognition. Lang Ling Compass 3, 128–156.
Greenhouse, S.W., Geisser, S., 1959. On methods in the analysis of profile data. Psychometrika 24, 95–112.
Groppe, D.M., Urbach, T.P., Kutas, M., 2011. Mass univariate analysis of event-related brain potentials/fields I: a critical tutorial review. Psychophysiology 48, 1711–1725.
Hemera Technologies Inc, 2002. Hemera Photo Objects.
Hollingshead, A.B., 1965. Two Factor Index of Social Position. Yale University Press, New Haven, CT.
Jacobs, R.A., Kruschke, J.K., 2011. Bayesian learning theory applied to human cognition. Wiley Interdiscip. Rev. Cogn. Sci. 2, 8–21.
Jaeger, T.F., Snider, N.E., 2013. Alignment as a consequence of expectation adaptation: syntactic priming is affected by the prime's prediction error given both prior and recent experience. Cognition 127, 57–83.
Javitt, D.C., 2009. When doors of perception close: bottom-up models of disrupted cognition in schizophrenia. Annu. Rev. Clin. Psychol. 5, 249–275.
Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276.
Kinoshita, S., 2000. The left-to-right nature of the masked onset priming effect in naming. Psychon. Bull. Rev. 7, 133–141.
Kleinschmidt, D.F., Jaeger, F.T., 2015. Robust speech perception: recognize the familiar, generalize to the similar, and adapt to the novel. Psychol. Rev. 122, 148–203.
Koester, D., Schiller, N., 2008. Morphological priming in overt language production: electrophysiological evidence from Dutch. NeuroImage 42, 1622–1630.
Kreher, D.A., Holcomb, P.J., Goff, D., Kuperberg, G.R., 2008. Neural evidence for faster and further automatic spreading activation in schizophrenic thought disorder. Schizophr. Bull. 34, 473–482.
Kreher, D.A., Goff, D., Kuperberg, G.R., 2009. Why all the confusion? Experimental task explains discrepant semantic priming effects in schizophrenia under "automatic" conditions: evidence from event-related potentials. Schizophr. Res. 111, 174–181.
Kuperberg, G.R., 2010a. Language in schizophrenia part 1: an introduction. Lang Ling Compass 4, 576–589.
Kuperberg, G.R., 2010b. Language in schizophrenia part 2: what can psycholinguistics bring to the study of schizophrenia… and vice versa? Lang Ling Compass 4, 590–604.
Kuperberg, G.R., Ditman, T., Kreher, D.A., Goldberg, T.E., 2009. Behavioral and electrophysiological approaches to understanding language dysfunction in neuropsychiatric disorders: insights from the study of schizophrenia. In: Wood, S.J., Allen, N.B., Pantelis, C. (Eds.), The Neuropsychology of Mental Illness. Cambridge University Press, New York, pp. 67–95.
Kutas, M., Federmeier, K.D., 2011. Thirty years and counting: finding meaning in the N400 component of the event-related brain potential (ERP). Annu. Rev. Psychol. 62, 621–647.
Kuznetsova, A., Brockhoff, P.B., Christensen, R.H.B., 2015. Tests for random and fixed effects for linear mixed effect models (lmer objects of lme4 package). R package version 2.0–33. http://cran.r-project.org/package=lmerTest.
Leitman, D.I., Sehatpour, P., Higgins, B.A., Foxe, J.J., Silipo, G., Javitt, D.C., 2010. Sensory deficits and distributed hierarchical dysfunction in schizophrenia. Am. J. Psychiatr. 167, 818–827.
Levelt, W.J.M., 1993. Speaking: From Intention to Articulation. MIT Press, Cambridge.
Levelt, W.J.M., Roelofs, A., Meyer, A.S., 1999. A theory of lexical access in speech production. Behav. Brain Sci. 22, 1–38 (Discussion 38–75).
Luck, S.J., 2014. Online Chapter 13: The Mass Univariate Approach and Permutation Statistics (An introduction to the event-related potential technique). MIT press, MIT Press Online.
Luck, S.J., Gaspelin, N., 2017. How to get statistically significant effects in any ERP experiment (and why you shouldn't). Psychophysiology 54, 146–157.
Lupker, S.J., 1979. The semantic nature of response competition in the picture-word interference task. Mem. Cogn. 7, 485–495.
Mahon, B.Z., Costa, A., Peterson, R., Vargas, K.A., Caramazza, A., 2007. Lexical selection is not by competition: a reinterpretation of semantic interference and facilitation effects in the picture-word interference paradigm. J. Exp. Psychol. Learn. Mem. Cogn. 33, 503–535.
Maris, E., Oostenveld, R., 2007. Nonparametric statistical testing of EEG- and MEG-data. J. Neurosci. Methods 164, 177–190.
McKenna, P.J., Oh, T.M., 2005. Schizophrenic Speech: Making Sense of Bathroots and Ponds that Fall in Doorways. Cambridge University Press, Cambridge, UK.
Meyer, D.E., Schvaneveldt, R.W., 1971. Facilitation in recognizing pairs of words: evidence of a dependence between retrieval operations. J. Exp. Psychol. Gen. 20, 227–234.
Moritz, S., Mersmann, K., Kloss, M., Jacobsen, D., Andresen, B., Krausz, M., Pawlik, K., Naber, D., 2001. Enhanced semantic priming in thought-disordered schizophrenic patients using a word pronunciation task. Schizophr. Res. 48, 301–305.
Moritz, S., Woodward, T.S., Kuppers, D., Lausen, A., Schickel, M., 2003. Increased automatic spreading of activation in thought-disordered schizophrenic patients. Schizophr. Res. 59, 181–186.
Neely, J.H., 1991. Semantic priming effects in visual word recognition: a selective review of current findings and theories. In: Besner, D., Humphreys, G.W. (Eds.), Basic Processes in Reading and Visual Word Recognition. Erlbaum, Hillsdale, NJ, pp. 264–333.
Ober, B.A., Vinogradov, S., Shenaut, G.K., 1995. Semantic priming of category relations in schizophrenia. Neuropsychology 9, 220–228.
Oppenheim, G.M., Dell, G.S., Schwartz, M.F., 2010. The dark side of incremental learning: a model of cumulative semantic interference during lexical access in speech production. Cognition 114, 227–252.
Porcaro, C., Medaglia, M.T., Krott, A., 2015. Removing speech artifacts from electroencephalographic recordings during overt picture naming. NeuroImage 105, 171–180.
R Core Team, 2016. R: A Language and Environment for Statistical Computing. (ISBN 3-900051-07-0, Vienna, Austria).
Roelofs, A., 2004. Error biases in spoken word planning and monitoring by aphasic and nonaphasic speakers: comment on Rapp and Goldrick (2000). Psychol. Rev. 111, 561–572 (Discussion 573–580).
Rosinski, R., 1977. Picture-word interference is semantically based. Child Dev. 48, 643–647.
Rumelhart, D.E., Hinton, G.E., McClelland, J.L., 1986. A general framework for parallel distributed processing. In: Rumelhart, D.E., McClelland, J.L. (Eds.), Parallel Distributed Processing: Explorations in the Microstructure of Cognition. MIT Press,

Cambridge, MA, pp. 45–76.
Schiller, N., 2008. The masked onset priming effect in picture naming. Cognition 106, 952–962.
Spitzer, M., Braun, U., Hermle, L., Maier, S., 1993. Associative semantic network dysfunction in thought-disordered schizophrenic patients: direct evidence from indirect semantic priming. Biol. Psychiatry 34, 864–877.
Starreveld, P.A., La Heij, W., 1996. Time-course analysis of semantic and orthographic context effects in picture naming. J. Exp. Psychol. Learn. Mem. Cogn. 22, 896–918.
Vinogradov, S., Ober, B.A., Shenaut, G.K., 1992. Semantic priming of word pronunciation and lexical decision in schizophrenia. Schizophr. Res. 8, 171–181.
Weisbrod, M., Maier, S., Harig, S., Himmelsbach, U., Spitzer, M., 1998. Lateralised semantic and indirect semantic priming effects in people with schizophrenia. Br. J. Psychiatry 172, 142–146.