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When Proactivity Fails: An Electrophysiological Study of Establishing Reference in Schizophrenia

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ABSTRACT

BACKGROUND: Schizophrenia is characterized by abnormalities in referential communication, which may be linked to more general deficits in proactive cognitive control. We used event-related potentials to probe the timing and nature of the neural mechanisms engaged as people with schizophrenia linked pronouns to their preceding referents during word-by-word sentence comprehension.

METHODS: We measured event-related potentials to pronouns in two-clause sentences in 16 people with schizophrenia and 20 demographically matched control participants. Our design crossed the number of potential referents (1-referent, 2-referent) with whether the pronoun matched the gender of its preceding referent(s) (matching, mismatching). This gave rise to four conditions: 1) 1-referent matching ("Edward took courses in accounting but he . . ."); 2) 2-referent matching ("Edward and Phillip took courses but he . . . "); 3) 1-referent mismatching ("Edward took courses in accounting but she . . ."); and 4) 2-referent mismatching ("Edward and Phillip took courses but she . . .").

RESULTS: Consistent with previous findings, healthy control participants produced a larger left anteriorly distributed negativity between 400 and 600 ms to 2-referent matching than to 1-referent matching pronouns (the "Nref effect"). In contrast, people with schizophrenia produced a larger centroposterior positivity effect between 600 and 800 ms. Both patient and control groups produced a larger positivity between 400 and 800 ms to mismatching than to matching pronouns.

CONCLUSIONS: These findings suggest that proactive mechanisms of referential processing, reflected by the Nref effect, are impaired in schizophrenia, while reactive mechanisms, reflected by the positivity effects, are relatively spared. Indeed, patients may compensate for proactive deficits by retroactively engaging with context to influence the processing of inputs at a later stage of analysis.

Keywords: Comprehension, Discourse, ERPs, Language, Pronouns, Reference

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In order to communicate effectively, producers and comprehenders must draw on common sets of shared referents (1,2). For example, to understand even a simple sentence such as "Edward took courses in accounting but he didn't learn much," the comprehender must infer that the communicator intended the pronoun "he" to refer to "Edward." It is well established that people with schizophrenia struggle with referential processing and that this can impair social functioning. However, we know little about the mechanisms underlying such impairments. In healthy individuals, the ability to proactively hold potential referents (such as "Edward") over time, with the goal of linking them to subsequent words (such as "he"), may be related to more general mechanisms of proactive cognitive control, which are known to be impaired in schizophrenia (3,4). In this study, we used event-related potentials (ERPs) to ask whether people with schizophrenia are selectively impaired in their use of proactive mechanisms of linking referents with pronouns during word-by-word sentence comprehension.

In schizophrenia, problems of establishing reference have been well characterized in language production (5–11). They include an ambiguous use of pronouns (5–8) and an overall increase in the use of pronouns (9). These abnormalities tend to remain stable over time (12,13), and they can predict measures of social cognition (9,14). People with schizophrenia can also struggle with linking anaphors[1] to their preceding referents during language comprehension (15,16). This can contribute to social dysfunction, including difficulties following social conversations (17–19).

[1] An anaphor is an expression whose interpretation depends on another expression in the context. For example, in the sentence "Edward took courses in accounting but he didn't learn much," "he" is an anaphor that refers to the preceding referent, "Edward." If the comprehender links an anaphor to the particular referent(s) that was intended by the producer, "referential cohesion" is said to be established.

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Healthy adult comprehenders are thought to engage two broad sets of mechanisms to achieve referential cohesion. The first is proactive. Here, discourse context, along with stored real-world knowledge, is used to predict[2] (or preactivate) possible upcoming events or states, along with their associated referents (20–26). When encountering an anaphor in the bottom-up input, the comprehender must link it to just one of these preactivated referents, further enhancing activation of this referent and suppressing any competing preactivated alternative referents.

The process of maintaining predicted referents over time, and linking them to incoming anaphors, is associated with an ERP effect with a frontal, and sometimes left-lateralized, scalp distribution, which has been termed the "Nref effect" [see (27) for a review], where "N" refers to the more negative-going polarity of the waveform evoked by anaphors that are more difficult versus easier to link to their preceding referent(s) ("ref"). A smaller (less negative) Nref is evoked by anaphors that unambiguously match a specific referent that has been predicted with high probability, whereas a larger Nref is evoked by anaphors that are more difficult to link to a specific preceding referent (28–34) [e.g., by "he" in the sentence "Edward and Phillip took courses but he . . ." (31)], perhaps because of competition from preactivated alternative referents.[3]

The second set of mechanisms used to achieve referential cohesion are "reactive" and are triggered only when an anaphor is perceived as failing to match referent(s) that have been preactivated by the context. This initial perception of referential failure leads comprehenders to search outside their current focus of attention and engage in prolonged attempts to retrieve either a previously mentioned referent (and the context in which it was introduced) (35) or a novel referent (36) from longer-term episodic memory. This, in turn, may lead comprehenders to update their current representation of context with these newly retrieved referents.

In the ERP waveform, reactive mechanisms are associated with a set of late positive-going ERP components that have a widespread or centroposterior scalp distribution. Late posterior positivities (or P600s) are produced when incoming bottom-up information cannot be linked to any information that has been anticipated based on the context—that is, when new inputs are perceived as strongly violating contextual constraints (37–39). They may reflect continued attempts to establish coherence (39–42) by retrieving information from longer-term memory and updating the representation of context [or, more generally, the contents of working memory; see (43–45)]. In the case of referential processing, larger late positivities are evoked by anaphors that mismatch (vs. match) the gender of all referents in their immediate context (31,46,47). For example, a large late positivity is evoked by the pronoun "she" (vs. "he") in the sentence "Edward took courses in accounting but she/he . . . ," particularly when the task encourages the assessment of coherence (31,46). Late positivities may, in part, reflect retroactive attempts to establish coherence by retrieving novel referents from outside the current focus of attention [e.g., (48,49)].

Although the mechanisms underlying referential impairments in schizophrenia remain unclear, there is evidence from other cognitive domains that proactive mechanisms, functioning to hold goal-relevant information within working memory (WM) (50), are impaired, while reactive mechanisms are relatively preserved (3,4,51). Moreover, patients' performance in tasks that tap into general proactive WM mechanisms can predict referential impairments during language production (52–55), as well as other aspects of language comprehension that rely on retaining contextual information over time (56); see Boudewyn *et al.* (57) and Swaab *et al.* (58) for discussions of domain-general control mechanisms in relation to impairments in discourse processing in schizophrenia.

On the basis of this previous work, we hypothesized that in schizophrenia, earlier proactive neural mechanisms engaged in referential processing would be impaired, but later reactive referential mechanisms would be relatively spared. ERPs are particularly well suited for testing this hypothesis because their temporal resolution provides a direct neural index of sequentially processing individual words as sentences unfold in real time. We therefore measured ERPs as people with schizophrenia and demographically matched control participants read four types of sentences, presented word by word, and then judged their coherence (see Table 1).

To probe proactive referential mechanisms, we contrasted ERPs to 1-referent matching pronouns (e.g., "he" in "Edward took courses in accounting but he . . .") and 2-referent matching pronouns (e.g., "he" in "Edward and Phillip took courses in accounting but he . . ."). Based on previous work (31), we expected that this contrast would produce an Nref effect in control participants. We hypothesized that if proactive referential mechanisms are impaired in schizophrenia, patients would show a smaller Nref effect than control participants. To probe reactive referential mechanisms, we contrasted the 1-referent matching pronouns with both the 1-referent mismatching and the 2-referent mismatching pronouns

Table 1. Sentence Types and Stimuli Examples

Sentence Type	Example
1-Referent Gender Matching	In night school Edward took courses in accounting but he didn't learn much.
2-Referent Gender Matching	In night school Edward and Phillip took courses but he didn't learn much.
1-Referent Gender Mismatching	In night school Edward took courses in accounting but she didn't learn much.
2-Referent Gender Mismatching	In night school Edward and Phillip took courses but she didn't learn much.

[2] By prediction, we refer to an implicit, probabilistic process of preactivating upcoming information, at multiple levels of representation, in a graded fashion, rather than to a strategic or all-or-nothing mechanism (79).

[3] Note that in this example, "he" is referentially ambiguous. While the Nref is classically associated with referential ambiguities, it can also be evoked by nonambiguous anaphors [e.g., (33,34)]. Note also that similar anteriorly distributed negativities are associated with maintaining and/or attempting to select other types of predicted entities from competing preactivated alternatives, including individual lexical items (80,81), syntactic structures (82), event structures (69,70,83–86), and types of interpretation [(87–89), Experiment 1], see the Supplement for further discussion of the functional significance of this effect.

(e.g., "she" vs. "he" in "Edward took courses in accounting but she/he . . ."). Based on previous work using similar stimuli and a similar task (46), we expected that this contrast would reveal a posterior late positivity effect in healthy adults. Based on previous work suggesting that, despite proactive deficits, people with schizophrenia can still use high-level contextual information to influence later stages of processing (59,60), we hypothesized that the schizophrenia group would also produce a late positivity effect to these referential violations.

METHODS AND MATERIALS

Stimuli

A total of 120 two-clause sentences were constructed. The first clause introduced one character (1-referent) or two characters (2-referents, both of the same gender: 50% female, established using proper names). The second clause began with a pronoun that matched or mismatched the gender of these characters, giving rise to four sentence types, each with 30 items (Table 1). This fully crossed design prevented participants from knowing, on the basis of the context alone, whether the pronoun would match or mismatch a preceding referent: a mismatching referent was just as likely to occur in a 1-referent as in a 2-referent context. Because the 1-referent sentences were inherently shorter than the 2-referent sentences (due to the introduction of one rather than two characters), we added two additional words that did not alter sentence meaning to their first clause in order to match the total number of words prior to the pronoun across conditions.

Sentences were counterbalanced across four lists. To each list, we added 64 fillers without any pronouns. These introduced variety in the types of sentences viewed and reduced the chance that participants would adopt an explicit strategy of anticipating that pronouns would always be encountered at particular points in the experimental sentences.

Participants

Individuals meeting DSM-IV criteria for schizophrenia, assessed using the Structured Clinical Interview for DSM (61), were recruited from the Lindemann Mental Health Center, Boston. All but one were receiving stable doses of antipsychotic medication. Demographically matched volunteers, who were not taking psychoactive medication and who had no histories of psychiatric disorders, were recruited by advertisement. All participants were native, primarily monolingual English speakers who had not learned any other language before the age of five. All were right-handed (62,63), without histories of head trauma, neurological disorder, substance abuse within 3 months, or histories of substance dependence (as assessed using the DSM-IV). Written informed consent was obtained in all participants following the guidelines of the Massachusetts General Hospital and Tufts Medical Center Human Subjects Research Committees.

In the schizophrenia group, clinical assessments were carried out on the same day as the ERP study using the Scale for the Assessment of Positive Symptoms (64) and the Scale for the Assessment of Negative Symptoms (65). In all participants, working memory was assessed using a reading span task (66,67).

Initially, 26 control subjects and 24 people with schizophrenia were recruited. However, the ERP datasets of 6 control subjects and 8 participants with schizophrenia were subsequently excluded from analysis because of low behavioral accuracy (see Behavioral Data Analysis for exclusion criteria [3 control subjects; 5 patients]), excessive artifact (see ERP Data Analysis for exclusion criteria [2 control subjects]), or both of these (1 control subject; 3 patients). This left 20 control participants and 16 people with schizophrenia whose data are included in the analyses reported. Demographic, clinical, and reading span data are summarized in Table 2.

Stimulus Presentation and Task

ERP data collection took place at Tufts University. Participants sat in a dimly lit room while sentences were presented word-by-word (see Figure 1 and legend for details). Their task was to press one of two buttons after seeing a "?" cue to indicate whether they judged each sentence to be acceptable or not. Participants were given examples of each type of sentence and 10 practice trials.

ERP Recording

Twenty-nine electrodes were secured on the scalp surface by an elastic cap (Electro-Cap International, Inc., Eaton, OH) (see Figure 2). Electrodes were also attached below the left eye and at the outer canthus of the right eye to monitor vertical and horizontal eye movements, and on the left and right mastoids. Impedances were kept below 10 kΩ for the eyes and below 2.5 kΩ at other sites. The EEG signal was

Table 2. Demographic, Medication, Working Memory, and Symptom Measures

	Control Group	Schizophrenia Group	Comparison
n	20 (7 female)	16 (3 female)	
Age, Years	45.6 (8.0)	39.1 (12.7)	$t_{34} = 1.78, p = .09$
Premorbid IQ[a]	107.7 (8.8)	102.1 (9.6)	$t_{34} = 1.85, p = .07$
Parental SES[b]	3.2 (1.2)	2.7 (1.3)	$t_{30} = 1.13, p = .27$
Reading Span[c]	45.7 (5.8)	39.4 (5.0)	$t_{34} = 3.42, p < .01$
CPZ Equivalent[d]		432 (287.8)	
SAPS[e]		15.2 (15.8)	
SANS[f]		15.5 (14.2)	

Values are presented as mean (SD).

CPZ, chlorpromazine; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SES, socioeconomic status.

[a]Premorbid IQ was assessed using the North American Adult Reading Test (94).

[b]Parental SES was calculated using the Hollingshead index (95). Two control participants and two patients did not provide parental occupation.

[c]The reading span task constituted 60 one-clause, five-word sentences. Reading span was operationalized as the total number of words recalled [following (31,33)].

[d]CPZ equivalents were calculated following the International Consensus Study of Antipsychotic Dosing (96).

[e]Summary scores (sum of the global ratings) for SAPS (64) are given.

[f]Summary scores (sum of the global ratings) for SANS (65) are given.

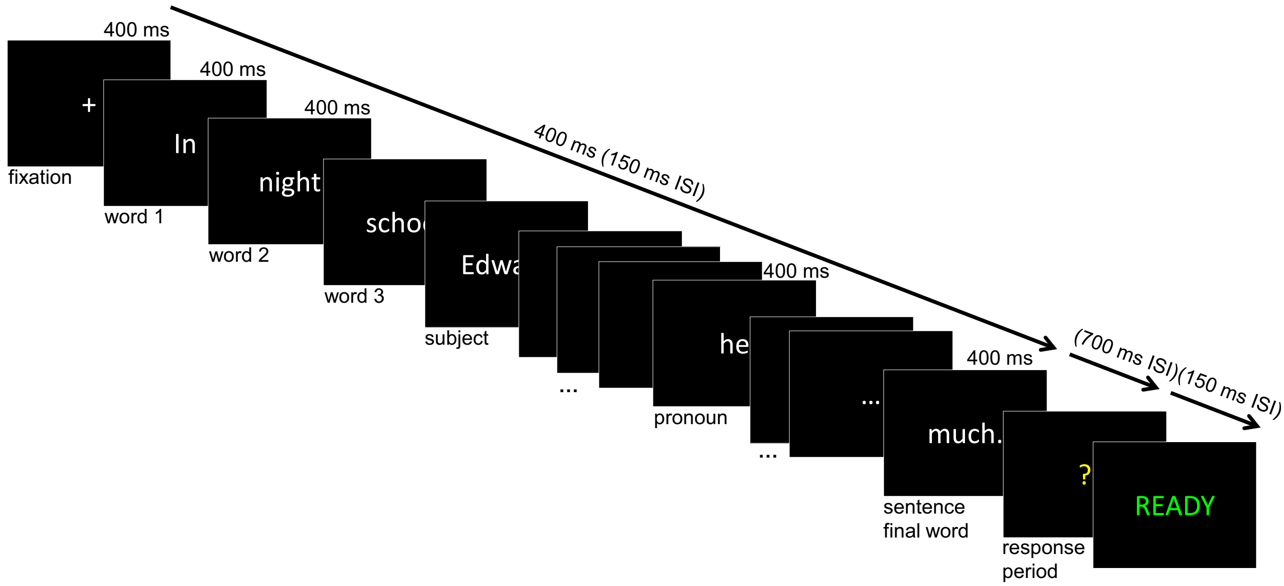

Figure 1. Trial presentation. The words were presented in white Arial font on a black background, with a viewing distance of 125 cm and a visual angle of 2 degrees. Each trial began with a fixation cross followed by the sentence, presented word by word. The fixation cross and each word was presented for 400 ms with an interstimulus interval (ISI) of 150 ms. The sentence-final word appeared with a period and was also presented for 400 ms but was followed by a 700 ms interstimulus interval, and then by a "?" that appeared in yellow font. This "?" cued participants to press either a "Yes" or "No" button, depending on whether they judged the sentence that they had just read to be acceptable. After participants made their response, the word "READY" in green font appeared on the screen. Participants then pressed a button to move them on to the next trial.

amplified by an Isolated Bioelectric Amplifier System Model HandW-32/BA (SA Instrumentation Co., San Diego, CA) with a bandpass of 0.01 to 40 Hz. It was continuously sampled at 200 Hz by an analog-to-digital converter, and was referenced online to the left mastoid.

Behavioral Data Analysis

We considered accurate responses as being "Yes" following the matching sentences and "No" following the mismatching sentences. A priori, we expected that these classifications would be more straightforward and less ambiguous for the 1-referent than the 2-referent sentences, and so we set a threshold such that if any participant responded with $<$60% accuracy in either of these two conditions, he or she was excluded. For included participants, the percentage of accurate responses was entered into a four-way analysis of variance (ANOVA) with sentence type as a within-subjects factor and group as a between-subjects factor. Significant effects were followed up with planned comparisons.

ERP Data Analysis

ERPs were averaged offline at each electrode site in each experimental condition. Trials contaminated by eye artifact or amplifier blockage were excluded. If, after artifact rejection, a participant had $<$18 remaining items in any one of the four conditions, his or her dataset was excluded. Of the participants included in the final analysis, artifact contamination led to the rejection of 18.7% of trials in the schizophrenia group and 18.3% of trials in the control group (no between-group difference, $p > .10$).

Analyses were conducted on the mean amplitudes of ERPs evoked by the pronouns, regardless of participants' judgments. In the schizophrenia group, but not the control group, examination of the waveforms using prestimulus (prepronoun) baselines of -200 to 0 ms and -100 to 0 ms revealed a divergence between ERPs evoked by the 1-referent matching pronouns and the pronouns in the other three conditions within the first 100 ms after pronoun onset. We attribute this to artifact in the prestimulus baseline period.[4] To reduce the chance that these early differences in the patient group would confound our planned between-group analyses of later effects, we chose to correct for them by carrying out all planned analyses using a post-stimulus baseline of 0 to 100 ms in all four conditions in both groups. However, to check that that this did not lead us to falsely infer significant late effects, we carried out and report selected post hoc analyses to determine whether effects remained significant when using a -200 to 0 ms prestimulus baseline.

[4] This differential activity between 0 and 100 ms in the schizophrenia group is unlikely to have reflected differences in perceptual processing across conditions of the pronouns, as these were identical across conditions. Similarly, differential activity within the prestimulus period is unlikely to have reflected true differences in anticipatory activity across these conditions prior to the onset of the critical pronoun. This is because, by design, the words that preceded the pronouns were identical between the matching and mismatching 1-referent sentences and between the matching and mismatching 2-referent sentences.

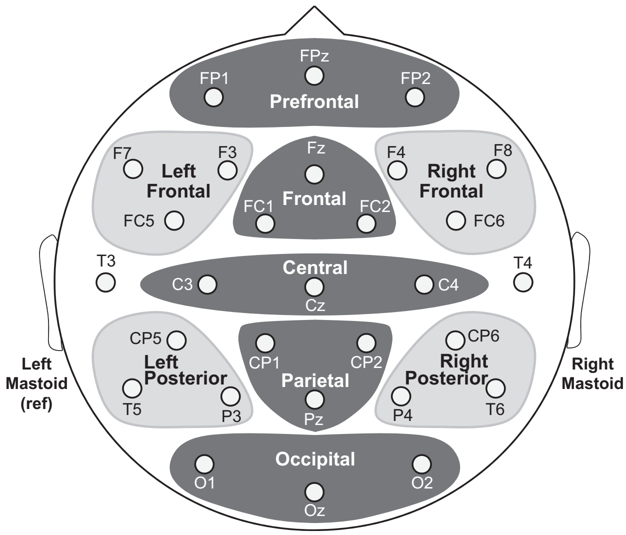

Figure 2. Electrode montage with regions used for analysis. For the purposes of statistical analyses, the scalp was divided into three-electrode regions. Regions in dark gray were part of the midregions omnibus analysis of variance and regions in light gray were part of the peripheral regions omnibus analysis of variance.

Planned ANOVAs focused on two time windows: 400 to 600 ms and 600 to 800 ms. Previous studies (29–33) show that the Nref effect in healthy control participants consistently falls within the first time window, sometimes extending to the second. The 600 to 800 ms window was selected on the basis on previous studies showing that it captures the late positivity and/or P600 effect, while minimizing component overlap from earlier negativity effects [e.g., (68)].

To gain comprehensive coverage of the scalp, we included region and hemisphere as spatial factors in omnibus ANOVAs that contrasted the 1-referent matching sentences with each of the three other sentence types, between the two groups.[5]

For each contrast, we carried out two omnibus ANOVAs, covering midregions (Figure 2, dark gray) and peripheral regions (Figure 2, light gray). In midregion analyses, the within-subject factors were sentence type and region (prefrontal, frontal, central, parietal, and occipital), and the between-subject factor was group (control, schizophrenia). In peripheral region analyses, we included an additional within-subject factor, hemisphere. In these omnibus analyses, we report only main effects and interactions involving sentence type, as we were primarily interested in group differences in how ERPs were modulated across conditions. Alpha was set to .05 for planned comparisons.[6] A Greenhouse-Geisser correction was applied to analyses with more than one *df* in the numerator (original *df* with corrected *p* values are reported).

Exploratory correlations between ERP effects of interest and 1) reading span scores within both the control and patient groups, and 2) selected clinical measures within the schizophrenia group are reported in the Supplement.

RESULTS

Behavioral Data

People with schizophrenia performed less accurately overall than control participants (control participants: 92%, SD: 7.4; patients: 83%, SD: 12.3; main effect of group, $F_{1,34} = 7.33$, $p < .01$), but the pattern of accuracy across the four types of sentences did not differ between the two groups (no interactions between group and sentence type, for all: $F < 0.6$, $p > .4$). Across both groups, there was a significant effect of sentence type, $F_{3,102} = 7.77$, $p < .0001$, due to lower accuracies in classifying the 1-referent mismatching sentences (84.8%, SD: 12.2) than the 1-referent matching sentences (91.5%, SD: 9.8), $F_{1,34} = 16.20$, $p < .0003$. There were no significant differences in accuracy between the 2-referent

[5] An alternative approach for comparing effects between patients and control participants would have been to carry out analyses only within spatial regions of interest where we expected to see maximal effects in the control group. This, however, would have potentially introduced type II error. For example, while we had strong a priori hypotheses that the healthy control participants would produce an Nref effect in the left frontal region, we were reluctant to compare control participants and patients only within this region. This is because any group differences in the effect identified here might lead us to infer that the Nref effect is reduced in patients compared with control participants. However, given that the Nref effect is not necessarily or always confined just to left frontal regions, this approach would exclude the possibility that patients did in fact produce an Nref effect over other frontal regions that were not examined at all. An omnibus ANOVA that includes spatial factors reduces this possibility. On the other hand, it comes at a cost: the number of tests and comparisons entailed means that any unpredicted effects at $p < .05$ within the schizophrenia group may be due to type I error (90). See footnote 6 and the Supplement for our approach to guard against this possibility.

[6] In the control group, we had strong a priori hypotheses about the location and nature of the ERP effects: we expected to see an Nref effect in comparing the 1-referent matching and the 2-referent matching pronouns within the left frontal region, and we expected to see a widespread late positivity effect in comparing the 1-referent matching pronouns with each of the two types of mismatching pronouns. Thus, for planned comparisons within these regions in the control group, an α of $p \leq .05$ is appropriate (as explained in footnote 5, if we had just considered the control participants, an omnibus test would not strictly be necessary: we could have proceeded straight to these planned comparisons to test these effects). An α level of $p \leq .05$, however, is less appropriate for testing the significance of effects in the schizophrenia group that were only resolved through hierarchical follow-up of our omnibus ANOVAs. This is because, although our approach allowed for full coverage of the scalp, it created multiple opportunities to detect effects, which increased the probability of type I error (90). This is particularly problematic for interpreting less well-characterized ERP effects. To address this issue, we carried out an additional mass univariate analysis, in combination with a cluster-based permutation test (91,92) to account for multiple comparisons, in the schizophrenia group. Details of these methods and results are reported in the Supplement.

matching sentences (85.8%, SD: 13.5) and the 2-referent mismatching sentences (88.9%, SD: 12.4), $F_{1,34}$ = 3.20, $p > .08$.

ERP Data

The 2-Referent Matching Versus 1-Referent Matching Pronouns. In control participants, but not in people with schizophrenia, the waveforms evoked by the 2-referent matching and the 1-referent matching pronouns appeared to diverge between 400 and 600 ms, particularly at left-lateralized frontal sites (Figure 3). In keeping with previous studies in control subjects [e.g., (28,29,31,33)], we interpret this as an Nref effect.

Group differences for this effect were reflected by three-way interactions among group, sentence type, and region (midregions: $F_{4,136}$ = 4.26, $p < .05$; peripheral: $F_{1,34}$ = 6.05, $p < .05$). In control participants, follow-ups revealed a three-way interaction among sentence type, region, and hemisphere in the peripheral regions ANOVA ($F_{1,19}$ = 4.78, $p < .05$) due to a significant interaction between region and sentence type over the left hemisphere ($F_{1,19}$ = 5.36, $p < .05$), but no effects over the right hemisphere ($p > .7$). This reflected the left-lateralized distribution of the Nref effect. Post hoc tests within the left frontal region using a −200 to 0 ms baseline confirmed significant effects at all sites in the control group. In the schizophrenia group, there were no main effects or interactions involving sentence type (for all: $p > .10$).

In the 600 to 800 ms window, control participants did not appear to show any ERP modulation. However, people with schizophrenia appeared to produce a larger positivity to the 2-referent matching than the 1-referent matching pronouns. This group difference was reflected by interactions between group and sentence type (midregions: $F_{1,34}$ = 5.78, $p < .05$; peripheral regions, marginal: $F_{1,34}$ = 2.72, $p < .10$). In the schizophrenia group, simple-effects ANOVAs revealed a larger widespread positivity to the 2-referent matching than the 1-referent matching pronouns (main effect of sentence type at midregions: $F_{1,15}$ = 5.43, $p < .05$; peripheral regions, marginal: $F_{1,15}$ = 3.82, p = .07), see also the Supplement for results of a mass univariate analysis. Post hoc tests in the schizophrenia group within parietal and occipital midregions using a −200 to 0 ms baseline confirmed significant effects at all sites in the schizophrenia group. No such differences were observed in the control group (no main effects of sentence type in either the midregions or peripheral regions analyses, $F_{1,19}$ = 0.14, $p > .7$ and $F_{1,19}$ = 0.25, $p > .6$, respectively).

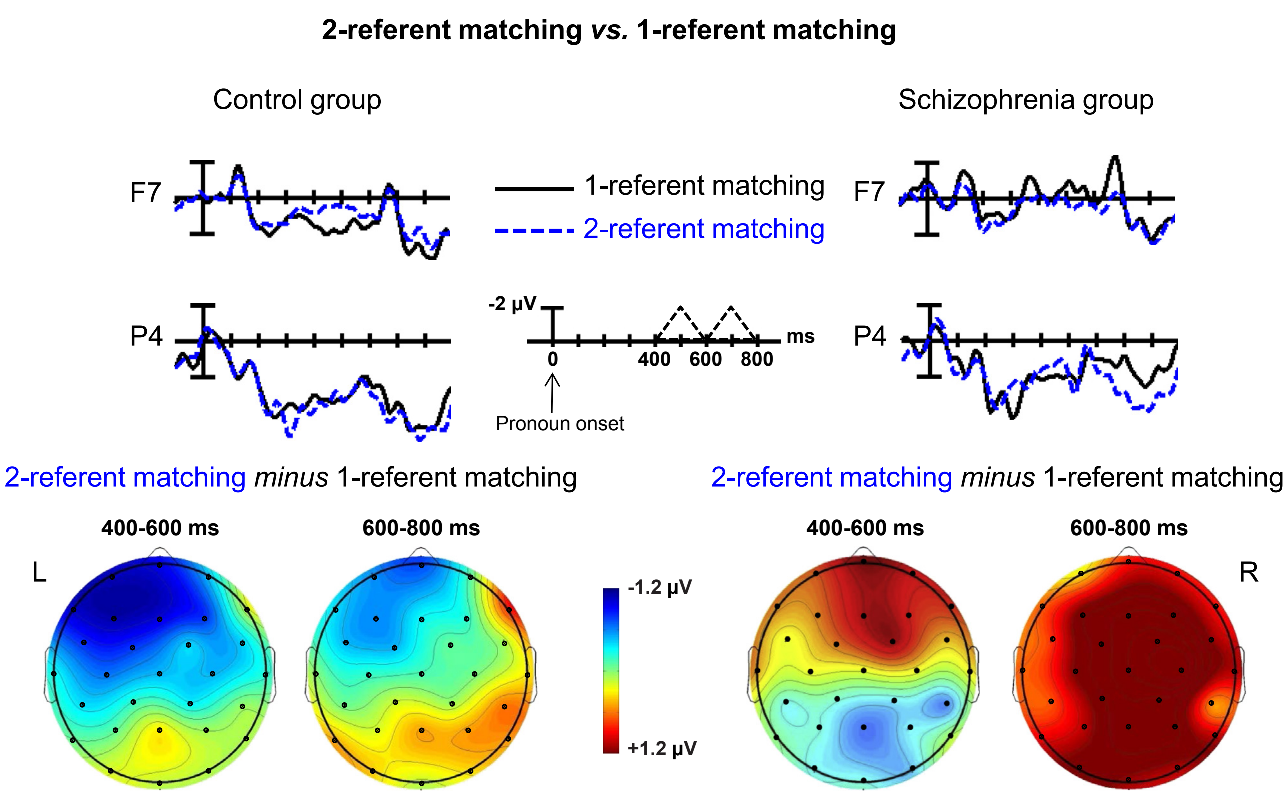

Figure 3. Contrast between 1-referent matching and 2-referent matching pronouns. (Top) Grand-averaged waveforms evoked by pronouns in the control and schizophrenia groups at a left frontal site (F7) and a right parietal site (P4). Solid black lines indicate event-related potentials (ERPs) to the 1-referent matching pronouns; dotted blue lines indicate ERPs to the 2-referent matching pronouns. Negative voltage is plotted upward in all ERP plots. (Bottom) Voltage maps show differences between ERPs evoked by the pronouns in these two conditions between 400 and 600 ms and between 600 and 800 ms. In the 400 to 600 ms time window, an Nref effect was seen in the control group but not in the schizophrenia group. In the 600 to 800 ms time window, a late positivity effect was seen in the schizophrenia group but not in the control group. L, left; R, right.

The 1-Referent Mismatching Versus 1-Referent Matching Pronouns. Between 400 and 600 ms, there was a significant main effect of sentence type across both groups at midregions, $F_{1,34} = 6.08$, $p < .05$, and in the later 600- to 800-ms time window, this effect approached significance at midregions: $F_{1,34} = 3.24$, $p = .08$. As shown in Figure 4A, this contrast was associated with a positivity effect in both groups, although the scalp distribution of these positivity effects differed between the two groups (for full report, see the Supplement).

The 2-Referent Mismatching Versus 1-Referent Matching Pronouns. Between 400 and 600 ms and 600 and 800 ms, there was a main effect of sentence type across both groups (400–600 ms: midregions: $F_{1,34} = 5.34$, $p < .05$; peripheral regions: $F_{1,34} = 4.35$, $p < .05$, 600–800 ms: midregions, $F_{1,34} = 4.14$, $p < .05$, and peripheral regions, $F_{1,34} = 6.23$, $p < .05$) (Figure 4B). As shown in Figure 4B, this contrast was associated with a positivity effect in both groups, although again the scalp distribution of these positivity effects differed between the two groups. Moreover, in the control but not the schizophrenia group, the positivity effect was accompanied by an anteriorly distributed negativity effect (see the Supplement for full report and discussion).

DISCUSSION

We exploited the excellent temporal resolution of ERPs to investigate the timing and nature of proactive and reactive mechanisms of establishing referential cohesion during language comprehension in healthy adults and people with schizophrenia. Control participants produced a larger left anteriorly distributed negativity between 400 and 600 ms to 2-referent matching than to 1-referent matching pronouns (the Nref effect). In contrast, people with schizophrenia failed to produce this effect, but instead produced a later positivity effect between 600 and 800 ms. Both groups produced a larger positivity between 400 and 800 ms to pronouns that mismatched versus matched the gender of their referent(s).

In control subjects, modulation of the Nref is thought to reflect the difficulty of linking an anaphor to a preceding referent. When encountering a pronoun that is consistent with a referent that has been predicted (preactivated) with high probability, it is easier to establish referential cohesion, and a smaller (less negative) Nref is produced. If additional competing referents have also been preactivated, however, it is harder to select the appropriate referent and establish referential cohesion, and a larger Nref is produced [for a related interpretation of other late negativity effects, see (68–70), and see the Supplement for further discussion of the functional significance of the Nref effect]. In schizophrenia, the reduced Nref modulation suggests that these proactive mechanisms of establishing referential cohesion are impaired. This may be because, in the 2-referent matching sentences, patients failed to use context to preactivate or proactively maintain both referents over a delay, leading to less competition when encountering the anaphor. Alternatively, they may have found it relatively difficult to process the 1-referent matching pronouns, either because they failed to preactivate the single referent with high probability or because they failed to use the incoming pronoun to select this referent.[7]

In contrast, reactive referential mechanisms appeared to be relatively spared in schizophrenia. Like control participants, people with schizophrenia produced a larger late positivity to gender mismatching than matching pronouns (although with different scalp distributions; see the Supplement for full report and discussion). We suggest that, when encountering the pronoun, patients engaged in initial attempts to link it to a referent within the immediate context, and, like control participants, they perceived the mismatch in gender between the pronoun and its referent(s) (31,46,47). This may have been reflected by the positivity effect between 400 and 600 ms. This then led to prolonged retroactive attempts to establish coherence (39,40), perhaps through attempts to retrieve novel referents (48,49) from episodic memory, outside the focus of attention, thereby updating the current representation of context (43,44). This may have been as reflected by the positivity effect between 600 and 800 ms.

In addition to producing a positivity effect to the gender mismatching (vs. matching) pronouns, people with schizophrenia, unlike the control participants, also produced a positivity effect between 600 and 800 ms to the 2-referent (vs. 1-referent) matching pronouns. In other words, they produced this later positivity effect instead of the earlier Nref effect (400–600 ms). This suggests not only that reactive mechanisms of establishing referential coherence were relatively preserved, but also that patients employed these mechanisms at a later stage of processing to compensate for their proactive deficits. This finding is strikingly consistent with the results of a previous ERP study of discourse comprehension in schizophrenia in which, instead of influencing modulation of an earlier ERP component (in that case, the N400), the discourse context influenced modulation of a late positivity between 700 and 1000 ms (59). It is also in line with other findings suggesting that although a predictive use of context is impaired in schizophrenia, given enough time, patients can still extract information within a discourse context to inform their final interpretations (60). Finally, it provides evidence against the argument that the absent Nref effect in the schizophrenia group simply reflected a failure to engage with the task or understand instructions.

[7] Another way of conceptualizing this is to posit that, in control participants, the Nref effect was primarily driven by a left anterior positive-going waveform that was evoked by the 1-referent matching pronouns when reference was successfully established. On this account, the absent Nref effect in the schizophrenia group resulted from a failure to produce this positivity to the 1-referent matching pronouns, due to failure to quickly establish reference. This account is consistent with the pattern of waveforms across conditions, which does indeed suggest that a smaller positivity was produced by the 1-referent matching pronouns in the schizophrenia than in the control group (see Figure 3). On the other hand, given the difficulty of interpreting the absolute polarity of any ERP response (in relation to baseline) evoked in individual conditions, particularly in comparing patients and control participants [see (93), pages 73–74 for discussion], this observation should be interpreted with caution.

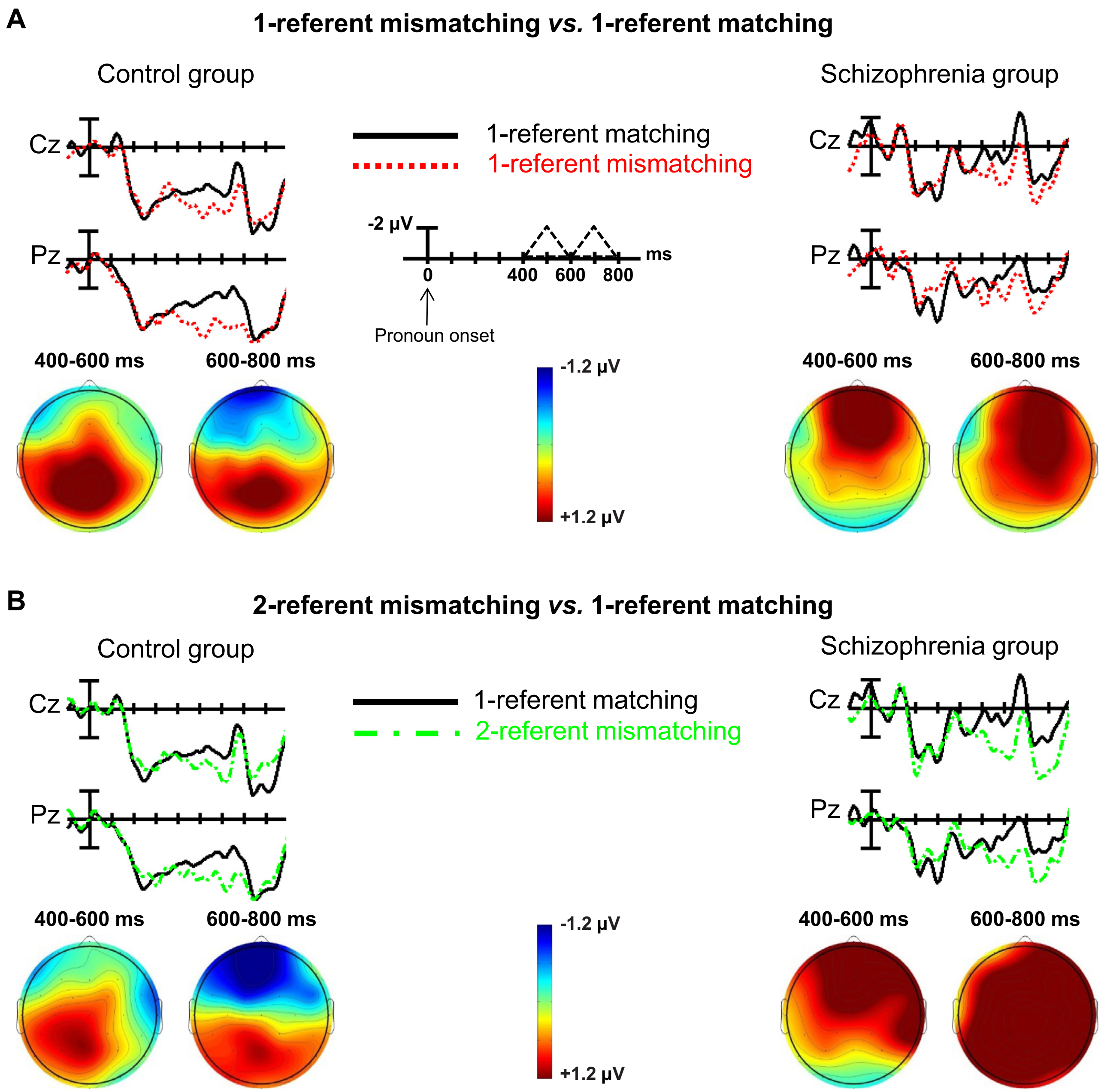

Figure 4. Contrasts between 1-referent matching and the two types of mismatching pronouns. **(A)** The 1-referent mismatching vs. 1-referent matching sentences. Grand-averaged waveforms evoked by pronouns in the control and schizophrenia groups at Cz and Pz. Solid black lines indicate event-related potentials (ERPs) to the 1-referent matching pronouns; dotted red lines indicate ERPs to the 1-referent mismatching pronouns. Negative voltage is plotted upward in all ERP plots. Voltage maps show differences between ERPs evoked by the 1-referent mismatching and 1-referent matching pronouns between 400 and 600 ms and 600 and 800 ms. **(B)** The 2-referent mismatching vs. 1-referent matching sentences. Grand-averaged waveforms evoked by pronouns in the control and schizophrenia groups at Cz and Pz. Solid black lines indicate ERPs to the 1-referent matching pronouns; dashed green lines indicate ERPs to the 2-referent mismatching pronouns. Negative voltage is plotted upward in all ERP plots. Voltage maps show differences between ERPs evoked by the 2-referent mismatching and 1-referent matching pronouns between 400 and 600 ms and 600 and 800 ms.

Our findings are consistent with the theory that schizophrenia is characterized by deficits of proactive cognitive control and WM (3,4). As shown in Table 2, reading span scores in the schizophrenia group were significantly smaller than in the control participants, although, unlike in previous studies in healthy adults (31,33), there were no significant correlations between the Nref and reading spans in either group, likely due to restricted individual variability (see the Supplement). More generally, our findings are consistent with the idea that predictive impairments in schizophrenia can explain and unify multiple abnormalities of language comprehension and production (71). It will, however, be important to replicate the present study in a larger sample and to determine whether referential impairments vary across subpopulations within schizophrenia.

Our findings also have social implications. Some researchers have discussed referential impairments in schizophrenia as stemming from a social communicative failure—a failure to take the communicator's assumptions into account (7,8,72) [see also (73,74)]. In practice, however, given the speed of everyday communication, establishing and drawing on common referents in real time will depend largely on the speed at which both the comprehender and producer can access relevant information from memory [see (75–78)]. In healthy individuals, this relies heavily on the ability to predictively mobilize contextual information [see (79) for a review]. Although it is encouraging that people with schizophrenia can engage reactive mechanisms to compensate for proactive deficits, reactive mechanisms tend to be slower and less efficient than predictive processing. Therefore, in most situations, there may not be enough time to engage them and still keep up with the fast pace of everyday conversation. Thus, our findings may, at least in part, help explain why patients struggle with social communicative interactions.

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