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

Supplemental Information

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Mass Univariate Analysis: Late Positivity effect in contrasting the 2-referent matching and the 1-referent matching pronouns in the schizophrenia group

As described in the main text, our omnibus ANOVA revealed a difference between the schizophrenia and the control group in comparing 2-referent matching and 1-referent matching pronouns between 600-800ms. This appeared to be due to the production of a late positivity effect in the schizophrenia group, but not the control group. Follow-ups within the schizophrenia group appeared to revealed a significant main effect of Sentence Type in the mid-regions ANOVA, $F(1, 15) = 5.43$, $p < .05$, and an effect that approached significance in the peripheral regions ANOVA, $F(1, 15) =3.82$, $p=.07$. As discussed by Luck and Gaspelin (2017) (1), however, this type of omnibus ANOVA approach, while allowing for full coverage of the scalp, creates multiple opportunities to detect an effect (i.e., a main effect and an interaction with Region), which increases the probability of Type I error. This is particularly problematic for ERP effects that have not been well characterized, such as this positivity effect in the schizophrenia group (although see (2) for a similar finding). To address this issue, we carried out a Mass Univariate Analysis in the patient group to see if the effect remained significant. With a mass univariate approach, separate tests are carried out at all time points at all electrode sites within specified time regions and spatial regions of interest, with a correction to account for multiple comparisons (3). It therefore explicitly accounts for multiple comparisons while retaining the ability to localize ERP effects on the scalp surface (4). 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).

To carry out this analysis, we used the Mass Univariate ERP Toolbox (3) and Factorial Mass Univariate ERP Toolbox (6). We first carried out a 1-way repeated measures ANOVA that compared all four sentence types in the schizophrenia group at all 40 sampling points between

600-800ms at each of 17 electrode sites (FC5, FC1, FC2, FC6, C3, Cz, C4, CP5, CP1, CP2, CP6, P3, Pz, P4, O1, Oz, O2), in each participant. Consecutive data points at electrodes within 8cm of one another (assuming a head diameter of 56cm) that exceeded a pre-set uncorrected p-value of 0.05 or less were considered clusters. The individual F-statistics within each cluster were summed to yield a cluster-level test statistics -- the cluster mass statistic.

Next, we randomly re-assigned the values across the four conditions at each sampling point at all 17 electrode sites within each participant, and calculated cluster-level statistics as described above. This was repeated 10,000 times. For each randomization, we took the largest cluster mass statistic, and, in this way, created a null distribution for the cluster mass statistic. Then we compared our observed cluster-level test statistic against this null distribution. Any clusters falling within the top 5% of the distribution were considered significant. This test revealed a cluster that was significant at $p = 0.021$, and which included all sites except for CP5, CP6, and P3, with a spatial cluster mass peak at C4, a temporal extent of 635-740ms and a temporal cluster mass peak at 670ms.

To follow-up this ANOVA, we carried out a planned repeated measures ANOVA that directly compared ERPs evoked by the 2-referent matching and the 1-referent matching pronouns in the patient group using a mass univariate approach (see (6) for discussion for why an F- rather than a t-test is more appropriate for this follow-up). This test was carried out within the same spatial and temporal region with similar parameters. It revealed a cluster that was significant at $p = 0.037$ at the same sites, and with the same cluster mass peak, with a temporal extent of 625-740ms and a temporal cluster mass peak at 640ms. This cluster reflected the larger positivity to the 2-referent matching than the 1-referent matching pronouns in the schizophrenia group.

Effects of referential violation: ERP results, discussion and supplementary tables

Results

These analyses contrasted the 1-referent matching pronouns with both the 1-referent mismatching and the 2-referent mismatching pronouns.

400-600ms: The results of the between-group omnibus ANOVAs are showed in Table S1. As shown in Figure 4 (main manuscript), both the control and schizophrenia groups produced positivity effects in contrasting the 1-referent matching pronouns with both the 1-referent mismatching and the 2-referent mismatching pronouns. However, the scalp distribution of these positivity effects differed between the two groups (3-way interactions between Group, Sentence Type and Region in both ANOVAs). To further characterize the sources of these interactions, we examined these contrasts in each group separately.

The findings in the control group are summarized in Table S2. The positivity effect evoked by the 1-referent mismatching (versus the 1-referent matching) pronouns was widespread but larger at posterior regions (interactions between Sentence Type and Region in both mid-regions and peripheral ANOVAs; effects at central, parietal, and left posterior regions). The positivity effect evoked by the 2-referent mismatching (versus the 1-referent matching) pronouns was less widespread and had a left posterior focus (Sentence Type x Region interactions in both mid-regions and peripheral ANOVAs; significant effects in the left posterior region).

The findings in the schizophrenia group are summarized in Table S3. In people with schizophrenia, the positivity effect evoked by the 1-referent mismatching (versus the 1-referent matching) pronouns was anteriorly distributed (Sentence Type x Region interactions in mid-regions ANOVA; effects in prefrontal and frontal regions). The positivity effect evoked by the 2-referent mismatching (versus the 1-referent matching) pronouns had a more widespread distribution (effect of Sentence Type approached significance in mid-regions omnibus ANOVA).

600-800ms: As shown in Figure 4 (main manuscript), in both the control and schizophrenia groups, these positivity effects continued into this later time window (1-referent matching versus 1-referent mismatching: marginal main effect in mid-regions ANOVA: 1-referent matching vs. 2-referent mismatching: main effects in both the mid-regions and peripheral regions ANOVAs, see Table S1). Once again, the scalp distribution of these positivity effects appeared to differ between the two groups, and, in the control group there appeared to be an anterior left-lateralized negativity effect within this time window, particularly in comparing the 2-referent mismatching and 2-referent matching pronouns. These differences were reflected by 3-way interactions between Group, Sentence Type and Region approaching or reaching significance in all ANOVAs (see Table S1). To further characterize the sources of these interactions, we examined these contrasts in each group separately.

The findings in the control group are summarized in Table S2. The late posterior positivity effect produced by the 1-referent mismatching (versus 1-referent matching) pronouns had a posterior, slightly left lateralized scalp distribution (interaction between Sentence Type and Region in the mid-regions ANOVA; interaction between Sentence Type, Region and Hemisphere in the peripheral regions ANOVA; effects in parietal and left posterior regions). The late posterior positivity effect produced by the 2-referent mismatching (versus 1-referent matching) pronouns also appeared to continue into this later window (interactions between Sentence Type and Region in both mid-regions and peripheral regions ANOVAs, although the positivity did not reach significance in any individual region). For this contrast, the presence of an anteriorly left-lateralized negativity effect was reflected by effects within prefrontal and left anterior regions.

The findings in the schizophrenia group are summarized in Table S3. The positivity effect evoked by the 1-referent mismatching (versus 1-referent matching) pronouns became more widespread in this time window (main effect of Sentence Type that approached significance at the mid-regions ANOVA; effects in central and parietal regions). Similarly, the positivity evoked by the 2-referent mismatching (versus 1-referent matching) pronouns became more widespread in this time window (main effect of Sentence Type in both mid-regions and peripheral regions ANOVAs; effects that reached or approached significance at all except the prefrontal region). Unlike in controls, there was no hint of an anteriorly distributed negativity effect in either of these contrasts in this time window.

Discussion

Findings in healthy controls

In controls, the presence of a posteriorly-distributed positivity effect in contrasting the 1-referent matching and 1-referent mismatching pronouns replicates previous findings (7, Experiment 2, 8). Here we also show that this effect is also produced when the 1-referent matching pronouns are contrasted with the 2-referent mismatching pronouns. In this latter contrast, however, the posterior positivity effect was accompanied by a left lateralized anterior negativity effect — an Nref effect.[1] This effect was most evident between 600-800ms, but it appears to have started within the 400-600ms time window (see Figure 4B). This provides evidence that the Nref effect is not specifically associated with contrasting referentially ambiguous and non-ambiguous anaphors (such as the contrast between the 2-referent matching ambiguous pronouns and 1-referent matching unambiguous pronouns, described in the main text

[1] The relationship between these two effects in this contrast is unclear. One possibility is that both the Nref and positivity effects were produced on single trials. Other possibilities are that these responses varied between participants, that they varied within participants on single trials, and/or that they varied across the course of the experiment, see (9) for discussion.

and shown in Figure 3, left), which is how the effect was first characterized (8, 10-13). A larger Nref can also be produced in response to non-ambiguous anaphors that are relatively more difficult to link to a specific preceding referent (see also (13, 14)), even when these referents violate gender constraints.

We suggest that a critical factor that influences the modulation of the Nref effect is the number of potential referents for which the context (and task) constrains. If a higher number of potential referents have been pre-activated, there will be more competition as participants attempt to select an appropriate referent upon encountering an anaphor, leading to a larger, or more prolonged, Nref. This interpretation links the Nref to other anteriorly-distributed negativity effects that are also modulated by the number of entities for which a context constrains: larger anterior negativity, sometimes with left lateralized distributions, are evoked by inputs when they are preceded by contexts that constrain for two or three medium probability entities relative to than when they are preceded by contexts that constrain for just one high probability entity (see (9, 15, 16) for discussion). These entities may be individual lexical items (17, 18), syntactic structures (19), event structures (9, 15, 16, 20-23), or types of interpretation (24, 25, 26, Experiment 1).

Findings in people with schizophrenia

In people with schizophrenia, the scalp distribution of the positivity effect produced in contrasting the 1-referent matching and the 1-referent mismatching pronouns was less posterior than in the controls: in the 400-600ms time window, the positivity effect was frontally distributed, and in the 600-800ms time window, it became more widespread. This was also true for the contrast between the 1-referent matching and the 2-referent mismatching pronouns.

One reason for this difference between the control and schizophrenia groups in the scalp distribution of the positivity effect may be differences in the degree of component overlap from the frontal negativity effect. As discussed above, in the control group, the positivity effect was accompanied by a frontal negativity effect, particularly in contrasting the 2-referent mismatching and the 1-referent matching pronouns in the 600-800ms time window. This frontal negativity effect may have obscured any appearance of a frontal positivity effect on the scalp surface, accounting for the posterior distribution of the effect. This explanation, however, does not account for why there was no hint of a posteriorly distributed positivity between 400-600ms in the schizophrenia group. Another (and not mutually exclusive) explanation is that the underlying neural generators of the positivity effects in the control and schizophrenia groups were distinct. It will be important to examine this possibility using techniques such as MEG that retain the temporal resolution of ERPs, but have better spatial resolution to detect underlying sources.

Regardless of why the scalp distribution of the positivity effect differed between the two groups, the clear absence of a negativity effect in contrasting the 1-referent mismatching the 2-referent mismatching pronouns in the schizophrenia group provides additional evidence that proactive referential processing was impaired in schizophrenia.

Supplementary Tables

Table S1. Between-group analysis. Results of the mid-regions and peripheral regions omnibus ANOVAs showing effects of Sentence Type as well as interactions between Sentence Type and Group, Region, and/or Hemisphere in contrasting the 1-referent matching pronouns with the 1-referent and 2-referent mismatching pronouns in the 400-600ms and 600-800ms time windows.

			400-600ms				**600-800ms**			
			1-referent matching vs. 1-referent mismatching		**1-referent matching vs. 2-referent mismatching**		**1-referent matching vs. 1-referent mismatching**		**1-referent matching vs. 2-referent mismatching**	
	Effect	*df*	*F*	*p*	*F*	*p*	*F*	*p*	*F*	*p*
Mid-regions omnibus ANOVA	S	1, 34	6.08	0.02*	5.34	0.03*	3.24	0.08^	4.14	0.05*
	SxG	1, 34	0.08	0.78	0.99	0.33	2.20	0.15	5.26	0.03*
	SxRxG	4, 136	4.56	0.01**	3.46	0.03*	1.67	0.19	3.95	0.02*
Peripheral regions omnibus ANOVA	S	1, 34	2.27	0.14	4.35	0.05*	2.75	0.11	6.23	0.02*
	SxG	1, 34	0.01	0.91	2.13	0.15	0.64	0.43	6.05	0.02*
	SxRxG	1, 34	7.60	0.01**	4.95	0.03*	1.18	0.29	4.46	0.04*
	SxHxG	1, 34	0.72	0.40	3.40	0.07^	2.12	0.16	0.26	0.62
	SxRxHxG	1, 34	0.02	0.89	0.33	0.57	0.19	0.67	0.13	0.72

S = Sentence Type, G = Group, R = Region, H = Hemisphere. Significant effects are indicated using the following symbols: ^ $p < .10$. *$p < .05$. **$p < .01$.

Table S2. Control group. Results of the mid-regions and peripheral regions omnibus ANOVAs showing effects of Sentence Type as well as interactions between Sentence Type, Region, and/or Hemisphere in contrasting the 1-referent matching pronouns with the 1-referent and 2-referent mismatching pronouns in the 400-600ms and 600-800ms time windows. Follow-ups of contrasts are also shown in individual regions.

			400-600ms				**600-800ms**			
			1-referent matching vs. 1-referent mismatching		**1-referent matching vs. 2-referent mismatching**		**1-referent matching vs. 1-referent mismatching**		**1-referent matching vs. 2-referent mismatching**	
	Effect	*df*	*F*	*p*	*F*	*p*	*F*	*p*	*F*	*p*
Mid-regions omnibus ANOVA	S	1, 19	3.72	0.07^	1.07	0.32	0.07	0.79	0.04	0.85
	SxR	4, 76	4.83	0.01**	2.15	0.12	5.50	0.01**	10.92	0.001***
Prefrontal	S	1, 19	0.36	0.56	0.22	0.64	2.53	0.13	5.27	0.03*
Frontal	S	1, 19	2.23	0.15	0.54	0.47	0.54	0.47	2.44	0.14
Central	S	1, 19	5.66	0.03*	1.85	0.19	0.79	0.39	0.04	0.84
Parietal	S	1, 19	13.81	0.001***	3.68	0.07^	6.31	0.02*	1.50	0.24
Occipital	S	1, 19	0.03	0.86	0.32	0.58	0.33	0.57	2.81	0.11
Peripheral regions omnibus ANOVA	S	1, 19	1.54	0.23	0.29	0.60	0.67	0.42	0.00	0.98
	SxR	1, 19	12.90	0.01**	6.20	0.02*	8.96	0.01**	23.21	0.001***
	SxH	1, 19	0.40	0.53	1.82	0.19	0.10	0.75	0.17	0.69
	SxRxH	1, 19	3.72	0.07^	2.68	0.12	5.05	0.04*	1.01	0.33
Left frontal	S	1, 19	0.19	0.67	0.14	0.71	1.84	0.19	4.51	0.05*
Right frontal	S	1, 19	0.04	0.85	0.25	0.62	0.02	0.88	1.85	0.19
Left posterior	S	1, 19	11.89	0.01**	5.84	0.03*	6.44	0.02*	3.25	0.09^
Right posterior	S	1, 19	2.21	0.15	0.25	0.62	2.09	0.16	2.05	0.17

S = Sentence Type, R = Region, H = Hemisphere. Significant effects are indicated using the following symbols: ^ $p < .10$. *$p < .05$. **$p < .01$. ***$p < .001$.

Table S3. Schizophrenia group. Results of the mid-regions and peripheral regions omnibus ANOVAs showing effects of Sentence Type as well as interactions between Sentence Type, Region, and/or Hemisphere in contrasting the 1-referent matching pronouns with the 1-referent and 2-referent mismatching pronouns in the 400-600ms and 600-800ms time windows. Follow-ups of contrasts are also shown in individual regions.

			400-600ms				**600-800ms**			
			1-referent matching vs. 1-referent mismatching		**1-referent matching vs. 2-referent mismatching**		**1-referent matching vs. 1-referent mismatching**		**1-referent matching vs. 2-referent mismatching**	
	Effect	*df*	*F*	*p*	*F*	*p*	*F*	*p*	*F*	*p*
Mid-regions omnibus ANOVA	S	1, 15	2.80	0.12	4.43	0.05^	3.76	0.07^	9.35	0.01**
	MxR	4, 60	3.90	0.03*	2.80	0.08^	1.46	0.25	2.46	0.12
Prefrontal	S	1, 15	7.31	0.02*	4.26	0.06^	1.00	0.33	1.35	0.26
Frontal	S	1, 15	5.71	0.03*	5.00	0.04*	2.69	0.12	6.35	0.02*
Central	S	1, 15	1.32	0.27	2.70	0.12	5.14	0.04*	10.62	0.01*
Parietal	S	1, 15	0.83	0.38	2.00	0.18	5.70	0.03*	15.71	0.001***
Occipital	S	1, 15	1.39	0.26	0.39	0.54	0.61	0.45	5.02	0.04*
Peripheral regions omnibus ANOVA	S	1, 15	0.86	0.37	4.33	0.06^	1.84	0.20	9.51	0.01**
	SxR	1, 15	0.94	0.35	1.21	0.29	0.43	0.52	0.02	0.90
	SxH	1, 15	0.32	0.58	1.56	0.23	4.42	0.05	0.85	0.37
	SxRxH	1, 15	0.65	0.43	0.08	0.78	1.05	0.32	1.09	0.31
Left frontal	S	1, 15	0.51	0.49	2.89	0.11	0.00	0.96	4.38	0.05^
Right frontal	S	1, 15	1.45	0.25	3.37	0.09^	2.07	0.17	4.07	0.06^
Left posterior	S	1, 15	0.14	0.71	1.16	0.30	1.17	0.30	15.21	0.001***
Right posterior	S	1, 15	0.15	0.70	3.82	0.07^	3.53	0.08^	6.76	0.02*

S = Sentence Type, R = Region, H = Hemisphere. Significant effects are indicated using the following symbols: ^ $p < .10$. *$p < .05$. **$p < .01$. ***$p < .001$.

Exploratory correlations between ERP effects of interest and WM span scores

Previous studies in young healthy adults have reported that individual behavioral measures of referential processing correlate with reading span measures (27), which, in part, tap into more general proactive control and working memory (WM) mechanisms (28). In addition, the magnitude of the Nref effect also correlates with reading span (8, 13). Finally, there is evidence that healthy individuals with low, but not high, reading spans produce late positivity effects, at least when the task encourages the establishment of referential coherence (see Experiment 1, (13)). In order to explore these relationships in the present study, we carried out correlations between reading span and ERP effects of interest in both the control and the schizophrenia groups. Note that, because of number of tests carried out, the relatively small sample sizes, and the restricted ranges in reading spans, these results should be considered preliminary.

Following Nieuwland and Van Berkum, and Engle and Kane (8, 13), we operationalized performance in the span task as the total number of words recalled. We correlated these scores with (a) the Nref effect evoked by the 2-referent matching minus the 1-referent matching pronouns between 400-600ms, averaged across left anterior electrode sites, F7, F3 and FC5, and (b) the positivity effects evoked by the 1-referent mismatching minus the 1-referent matching pronouns between 400-600ms and between 600-800ms, averaged across centro-parietal sites, Pz, CP1 and CP2.

We found no correlations between reading span scores and the magnitude of the Nref effect in either group (Pearson's $|rs| < .24$, $ps > .3$). We also found no correlations between reading span scores and the magnitude of the positivity effect between 400-600ms in either group (Pearson's $rs < .22$, $ps > .3$).

We did, however, see some evidence for associations between reading span scores and the magnitude of the late positivity effects evoked between 600-800ms in both the control and schizophrenia groups. The direction of this association was different in the two groups. In the control group, the correlation was negative (Pearson's $r = -0.454$; $p < 0.04$): those participants with lower reading span scores produced a larger late positivity effect. This is consistent with previous work (Experiment 1: (13)). In the schizophrenia group, however, the correlation was positive: those participants with lower reading span scores produced a smaller late positivity effect (Pearson's $r = 0.51$; $p < 0.04$). While these findings should be considered primary, it is possible that this reflects a failure of those patients with particularly poor WM function to retro-actively engage with context, leading to a failure to establish referential coherence altogether.

Exploratory correlations between ERP effects of interest and clinical measures within the schizophrenia group

Within the schizophrenia group, we also carried out post-hoc exploratory correlations between ERP effects of interest and various clinical measures: positive thought disorder, total SAPS, total SANS, duration of illness and chlorpromazine equivalents. Again, we correlated these measures with (a) the Nref effect evoked by the 2-referent matching versus the 1-referent matching pronouns between 400-600ms, averaged across left anterior electrode sites, F7, F3 and FC5, and (b) the positivity effects evoked by the 1-referent mismatching versus the 1-referent matching pronouns between 400-600ms and between 600-800ms, averaged across centro-parietal sites, Pz, CP1 and CP2. We found no significant correlations (ps > .08).

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