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Effects of DAR-0100A in individuals on cognitive deficits with schizophrenia

Yanran Li YL5465@CUMC.COLUMBIA.EDU
Department of Biostatistics
Columbia University

Abstract

Keywords: keyword one, keyword two, keyword three

1 Introduction

Schizophrenia (SCZ) is a complex psychiatric disorder characterized by a wide range of cognitive deficits, including but not limited to impairments in memory and attention. These deficits significantly contribute to the overall burden of the disease, affecting patients' daily functioning and quality of life. Traditional pharmacotherapy for schizophrenia has primarily focused on the management of psychotic symptoms, with less emphasis on the amelioration of cognitive impairments. However, the role of cognitive deficits in the disorder's pathology has garnered increased attention, highlighting the need for targeted treatment strategies.

Recent research suggests that dopamine dysregulation may play a critical role in the cognitive deficits observed in schizophrenia. Specifically, the dopamine D1 receptor subtype has been identified as a potential target for therapeutic intervention. Activation of D1 receptors is thought to facilitate cognitive processing, thereby offering a promising avenue for improving cognitive functions in individuals with schizophrenia.

In light of this, a randomized trial was conducted to explore the efficacy of DAR-0100A, a full, selective agonist of dopamine-1 receptors, in improving cognitive deficits in individuals diagnosed with schizophrenia. The study aimed to compare the cognitive outcomes of participants administered high doses (15mg), low doses (0.5mg) of DAR-0100A, and a placebo control group receiving normal saline. A total of 47 clinically stable schizophrenia patients were enrolled and randomized into one of the three treatment groups. The administration of DAR-0100A required an inpatient setting due to the risk of potential adverse effects, including fainting, necessitating careful monitoring.

The study design included multiple phases of drug administration and cognitive assessment. Participants underwent a baseline evaluation of cognitive function prior to the initiation of treatment. The treatment phase involved a 5-day period of DAR-0100A or placebo administration, followed by a cognitive assessment at the end of this phase. After a 10-day drug-free interval, the treatment was resumed for another 5 days, with a subsequent cognitive evaluation at the end of this period. Finally, a long-term follow-up assessment was conducted 90 days after the conclusion of the inpatient phase. Cognitive performance

was quantified using a composite memory score (MEM_Comp), providing a standardized measure of cognitive change across the study timeline.

This trial represents a critical step forward in the quest to address the cognitive deficits associated with schizophrenia, potentially offering new therapeutic avenues to enhance patient outcomes and quality of life.

2 Method

2.1 Data

In this dataset, 47 clinically stable individuals with SCZ were randomly assigned to one of three treatments: placebo (17 individuals), low dose DAR-0100A (14 individuals), or high dose DAR-0100A (16 individuals). We recorded the composite memory score on Days 0, 5, 19, and 90 as a numeric variable named `MEM_Comp`. Additionally, we collected age and gender data, represented by `Age` and `Gender`, respectively. While `Age` is a numeric variable, `Gender` is a factor variable with females as the reference group. Researchers were specifically interested in the treatment effects at day 5, 19, and 90, where we treated as categorical data.

The distributions of `MEM_Comp` stratified by Treatment and Time are plotted in Figure 2. The measured memory assessment scores from the high-dose treatment group are better than the other two compared groups. The trajectory of each patient stratified by Treatment and Time is also graphed as a spaghetti plot in Figure 3.

2.2 Model

We perform a linear mixed-effects model that incorporates patient-level correlation to investigate the treatment effect and its potential variation over time (in days). Each patient, denoted as i, undergoes four scheduled measurements, labeled as MEM_{ij}. The outcome, MEMdiff_{ij}, is a derived variable from MEM_{ij}, which represents the difference in MEM between each visit and the baseline visit (day 0), resulting in three observations per patient. Treatments are categorized as A, B, and C, corresponding to values 0, 1, and 2, respectively. The time variable, `Day`, is coded as 0, 1, and 2, representing measurements taken on days 5, 19, and 90. Treatment A and Day 5 serve as the reference group. Additionally, demographic factors such as age and gender are included in the model as covariates to address potential confounding effects.

$$\begin{aligned}\text{MEMdiff}_{ij} =& \beta_0 + \beta_1 \text{Age}_i + \beta_2 \text{Gender}_i + \\ & \sum_{t=1}^{2} \beta_{t+2} \times \text{I}\{\text{Treatment}_i = t\} + \sum_{d=1}^{2} \beta_{d+4} \times \text{I}\{\text{Day}_{ij} = d\} + \\ & \sum_{t=1}^{2}\sum_{d=1}^{2} \beta_{2(t-1)+d+6} \times \text{I}\{\text{Treatment}_i = t\} \times \text{I}\{\text{Day}_{ij} = d\} + b_{0i} + \epsilon_{ij}\end{aligned}$$

2.3 Missing Data

The missingness pattern in this data is drop-out missingness. Totally, there are 24 individuals who have complete observations at all four time points. If stratified by treatment

groups, there are 9 complete cases in the high-dose group, 7 complete cases in the low-dose group, and 8 complete cases in the placebo. Out of 47 subjects, 2 are missing on day 5, 12 are missing on day 19, and 16 are missing on day 90. The distribution of missing and present observations across various variables are shown in Figure 4, 5 & 6.

Generally, there are three types of missingness: Missing Completely at Random (MCAR), Missing at Random (MAR), and Missing not at Random (MNAR). MCAR assumes missingness is independent of other variables. We used a rigorous test for MCAR, the Little's test [Little (1988)], to test if the missingness in the dataset is MCAR or not. We got a p-value 0.008674472, so we have strong evidence to reject the null hypothesis (data is MCAR) and concluded the data is not from the MCAR assumption.

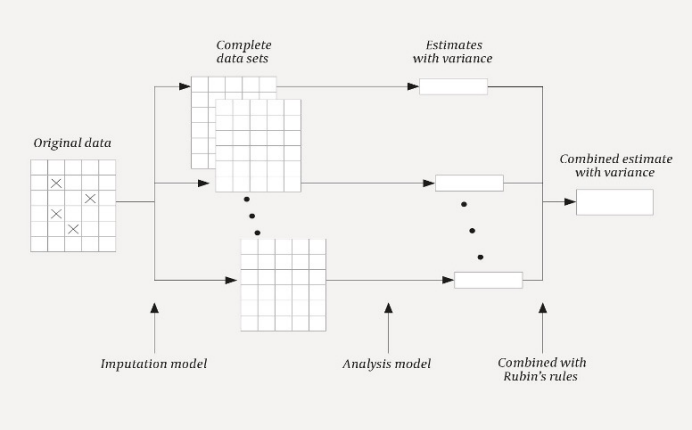
2.4 Imuptation

Assuming MNAR, we use multiple imputation with Linear Mixed Effects Model to investigate treatment effects and their variations over time. Referring to the processing chart in Figure 1, we performed imputation 6 times in our analysis.

2.4.1 Predictive Mean Matching

We imputed missing data with `mice` function in R, using **Predictive Mean Matching** for imputation. We calculate the predicted value of target variable according to specified imputation model ("Bayesian imputation under the normal linear model"). For each missing entry, this method forms a small set of candidates ("donors") from all complete cases that have the predicted values closest to the predicted value of missing entry. By randomly draw a donor, the observed value of the donor replaces the missing value. (Assuming the distribution of missing cell is the same as that of the observed value of donors [mic].)

Figure 1: Multiple Imputation for Missing Data



Our creation of multiple datasets introduces necessary variability reflective of the underlying uncertainty due to missingness. We then performed sensitivity analysis to examine the robustness of the statistical inferences under different missing data mechanisms. A predefined vector, δ, comprising values of -0.7, -0.2, 0.2, and 0.7, was constructed to simulate

various degrees of deviation from the MAR assumption-zero adjustment corresponds to the MAR assumption.

2.5 Analysis plan

For initial analysis, we initially overlook any missing data in the outcome variable. We employ both a likelihood ratio test and a Wald test to determine which treatment group exhibits a significant association with the MEM difference. Subsequently, we employ a likelihood ratio test to collectively evaluate whether the treatment effects vary over time, specifically examining interaction terms between treatment group and the time variable.

To assess the robustness of our model, we perform a sensitivity analysis that addresses the issue of missing values in the outcome variable for each patient. During this analysis, we follow the same inference procedure as previously outlined.

3 Result

3.1 MAR Assumption Model

Under the MAR assumption, our LMM model assessed the impact of various factors on the change in composite memory scores (MEM_diff) in SCZ patients. Table 1 indicated that age and gender (male) were not statistically significant predictors of memory score changes. Interestingly, the treatment with a high dose (15mg) of DAR-0100A (treatment_groupC) demonstrated a positive and statistically significant effect on memory scores compared to the placebo, suggesting potential cognitive benefits of the drug intervention. In contrast, the low dose (0.5mg) did not yield a significant difference. The assessments conducted on day 19 and day 90 showed no significant changes in memory scores, highlighting that the immediate post-treatment effects might not be sustained in the long term. The varying intercepts for individual subjects suggest that there were differences in baseline cognitive abilities among the patients, which the model accounted for. This analysis provides insights into the effectiveness of DAR-0100A for cognitive enhancement in clinically stable SCZ individuals and underscores the necessity of considering patient-specific factors in treatment response. Besides, in order to jointly test the interaction term between treatment groups and assessment days to determine if the timing of the treatment had different impacts on memory scores. We conducted ANOVA tests, which included the interaction terms alongside the main effects of age, gender, treatment group, and day. Seeing from Table 2, neither age nor gender showed a statistically significant effect on memory score changes. The treatment group factor approached statistical significance, suggesting a possible differentiation in the effectiveness of treatment between groups. However, the main effect of day did not show statistical significance, indicating that the time of assessment alone did not significantly impact memory scores.

3.2 Sensitivity Analysis

In our execution of sensitivity analysis, we evaluated the treatment effects on memory comparison scores under the MCAR assumption. The dataset was refined to include solely observations that were fully recorded, yielding what is termed the "completers" dataset. The precision and statistical significance of the parameters from our LMM models were

derived and Table 4 presents a concise summary of the model estimates, where coefficients for treatment groups specifically denote the average effect of each treatment, controlling for the other variables in the model. Table 5 shows a marginally significant effect on the difference in memory comparison scores ($p = 0.062105$). This indicates a potential difference in memory performance across the treatment groups, although the evidence is not strong enough to conclusively reject the null hypothesis at α level of 0.05. The interaction between treatment group and Day is not statistically significant ($p = 0.198262$), indicating that the effect of treatment on memory comparison scores does not significantly vary across different assessment days. The estimated coefficients (with 95% CI) of completers' LMM model are presented in Table 6.

The fixed effects from the pooled model results under each δ value are shown in Table 7, 8, 9 and 10. For each δ value, treatment C exhibits a significant difference from treatment A (the reference). Additionally, Table 11 suggests that we cannot reject the hypothesis indicating the adequacy of the crude model, implying that the interaction term between treatment group and day is not jointly significant. Hence, our conclusion aligns with the findings from the MAR case, indicating that the treatment effects exhibit no significant variation over time. This consistency underscores the robustness of our LMM model.

4 Conclusion & Discussion

In conclusion, our report aimed to elucidate the cognitive effects of DAR-0100A treatment at different dosages for individuals with SCZ, utilizing a LMM model to accommodate missing data and integrate baseline covariates and demographics such as age and gender. The evidence from our study indicates a promising efficacy of the high-dose DAR-0100A regimen in augmenting cognitive functions in SCZ patients. Conversely, the low-dose regimen did not exhibit a significant advantage over the placebo. Notably, our findings suggest that the impact of the treatment on cognitive abilities does not vary over time, which was affirmed by the consistency of treatment effects in a likelihood ratio test. The higher dose was consistently linked to significant improvements in MEM scores, while the lower dose was not. Sensitivity analyses makes sure the reliability of our primary model under the MNAR assumption, demonstrating its stability across multiple scenarios of bias.

References

https://cran.r-project.org/web/packages/miceRanger/vignettes/miceAlgorithm.html.

Roderick JA Little. A test of missing completely at random for multivariate data with missing values. *Journal of the American statistical Association*, 83(404):1198–1202, 1988.

Figure 2:

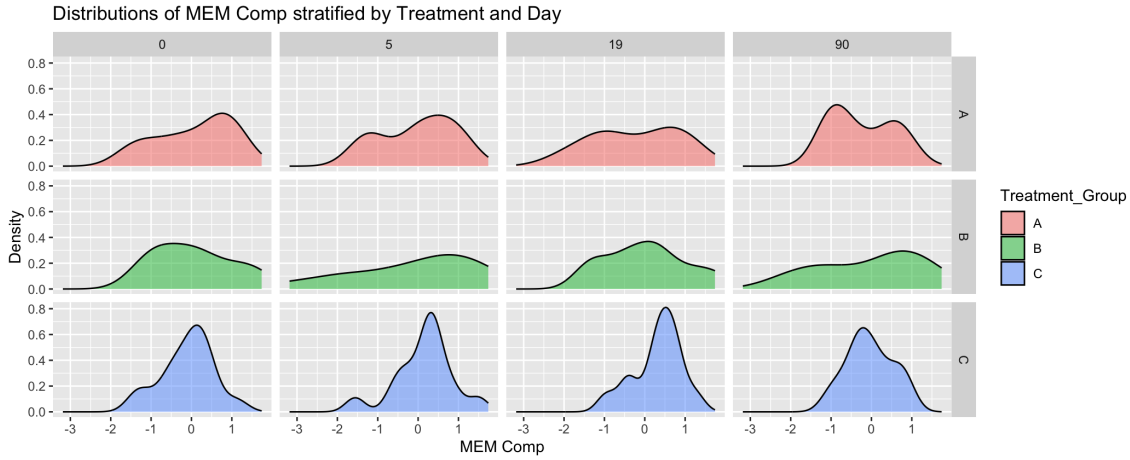


Table 1: Under MAR Assumption Model Summary Table

	Estimate	Std. Error	t value	p_value
(Intercept)	0.23	0.37	0.62	0.54
age	-0.01	0.01	-1.30	0.19
genderM	0.15	0.16	0.96	0.34
treatment_groupB	0.05	0.19	0.27	0.79
treatment_groupC	0.43	0.18	2.34	0.02
day19	0.05	0.09	0.51	0.61
day90	0.02	0.09	0.23	0.82

Table 2: Type III Anova Test

	Chisq	Df	Pr(>Chisq)
(Intercept)	0.75	1	0.3875
age	2.00	1	0.1576
gender	1.04	1	0.3090
treatment_group	5.56	2	0.0621
day	0.74	2	0.6903
treatment_group:day	6.00	4	0.1988

Figure 3: Spaghetti plot for longitudinal trajectory

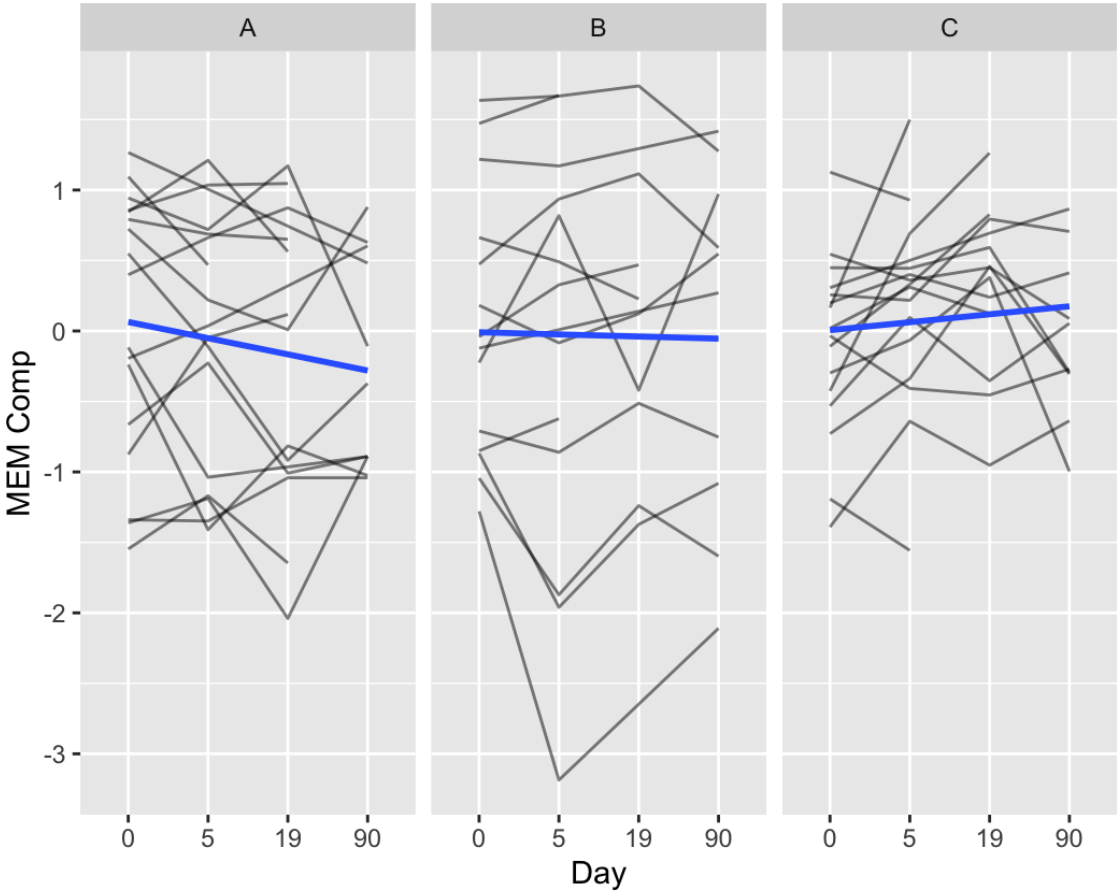


Figure 4: Total Missing `MEM_Comp` proportion

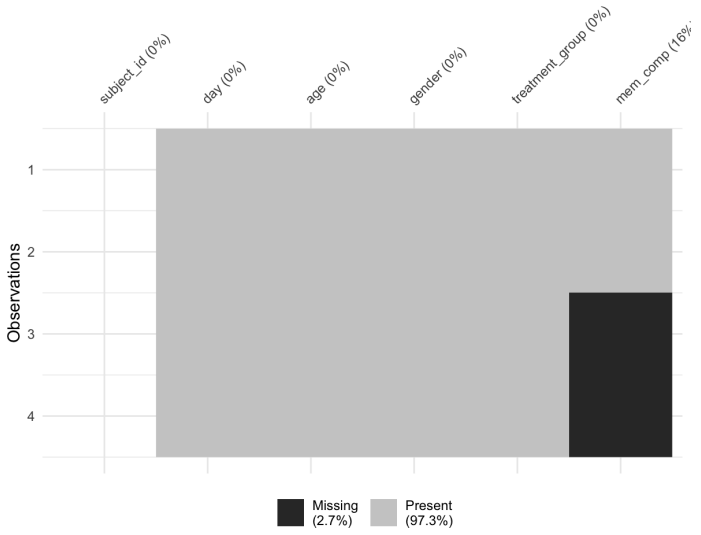


Figure 5: Missing `MEM_Comp` stratified by Day

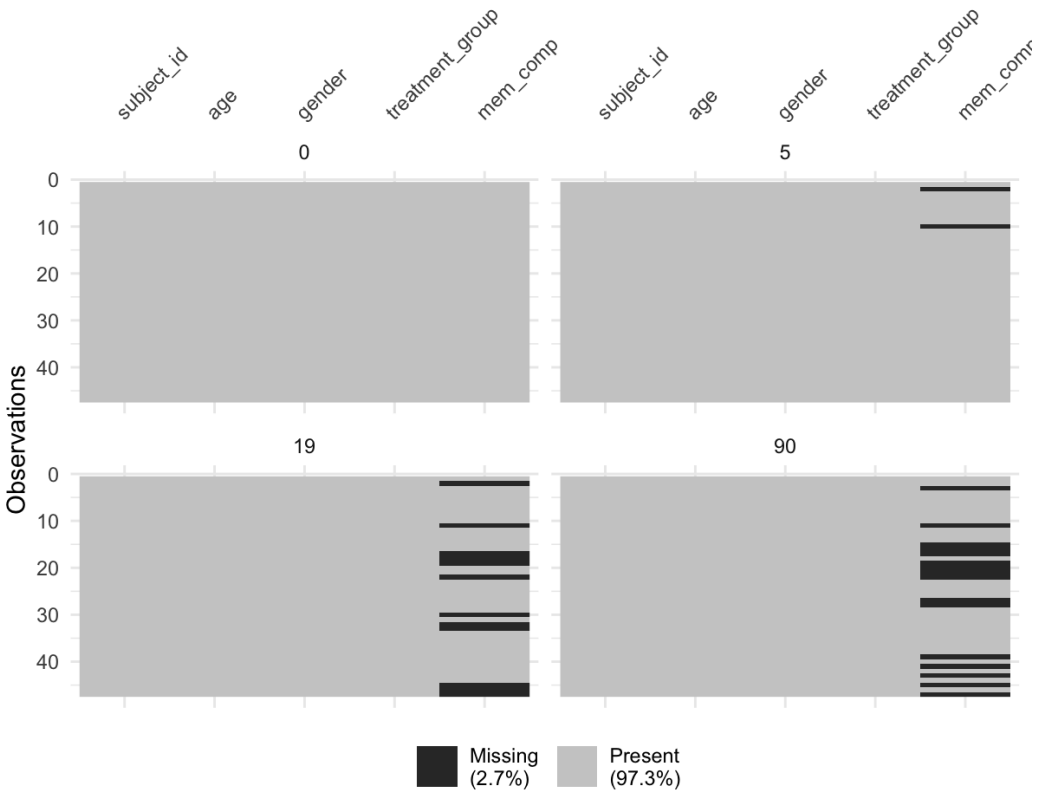


Table 3: Regression Summary Table under MAR assumption

Characteristic	Beta	95% CI[1]
Age	-0.011	(-0.029, 0.006)
Gender		
F	—	—
M	0.152	(-0.157, 0.461)
Treatment		
A	—	—
B	0.052	(-0.324, 0.428)
C	0.427	(0.069, 0.786)
Day		
5	—	—
19	0.046	(-0.131, 0.222)
90	0.022	(-0.164, 0.208)

Figure 6: Missing `MEM_Comp` stratified by Day

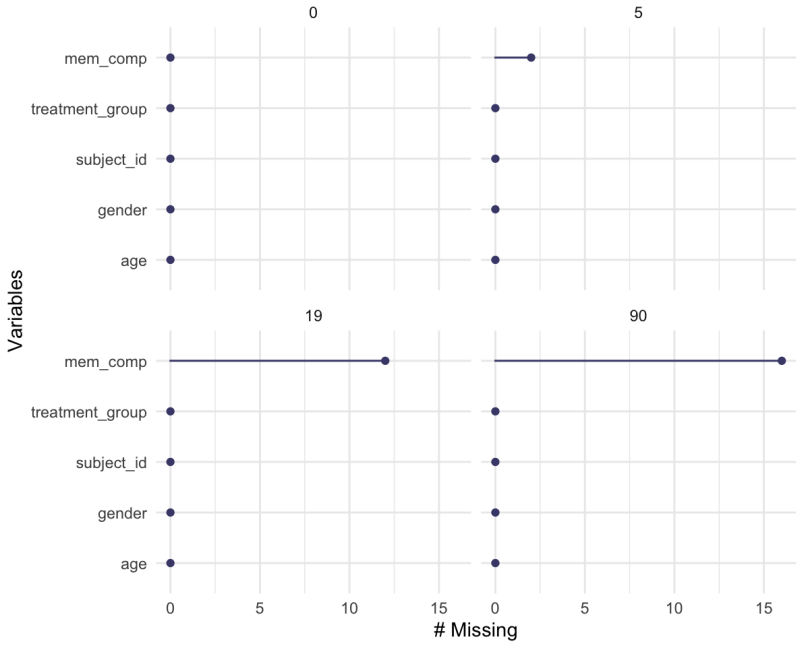


Table 4: Completers' Data Model Summary Table

	Estimate	Std. Error	t value	p_value
(Intercept)	-0.60	0.53	-1.12	0.27
age	0.01	0.01	0.55	0.58
genderM	0.06	0.20	0.32	0.75
treatment_groupB	0.29	0.24	1.18	0.24
treatment_groupC	0.44	0.22	1.97	0.05
day19	0.03	0.12	0.28	0.78
day90	-0.01	0.12	-0.05	0.96

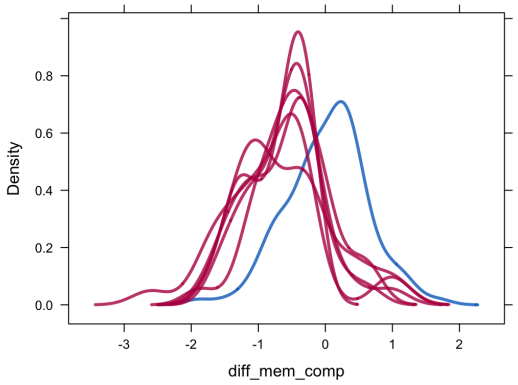
Table 5: Type III Anova Test

	Chisq	Df	Pr(>Chisq)
(Intercept)	0.75	1	0.3875
age	2.00	1	0.1576
gender	1.04	1	0.3090
treatment_group	5.56	2	0.0621
day	0.74	2	0.6903
treatment_group:day	6.00	4	0.1988

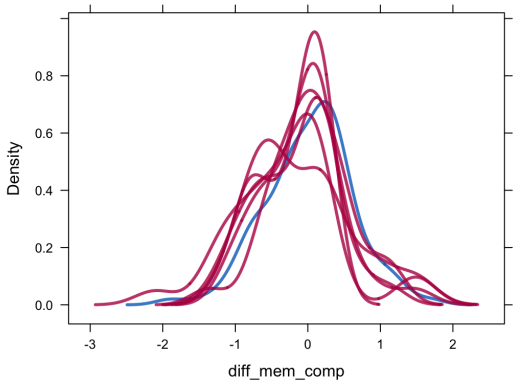
Table 6: Completers' Regression Analysis Coefficients

Characteristic	Beta	95% CI
Age	0.007	(-0.017, 0.031)
Gender		
F	—	—
M	0.064	(-0.324, 0.452)
Treatment		
A	—	—
B	0.287	(-0.189, 0.763)
C	0.437	(0.003, 0.871)
Day		
5	—	—
19	0.033	(-0.196, 0.262)
90	-0.006	(-0.235, 0.224)

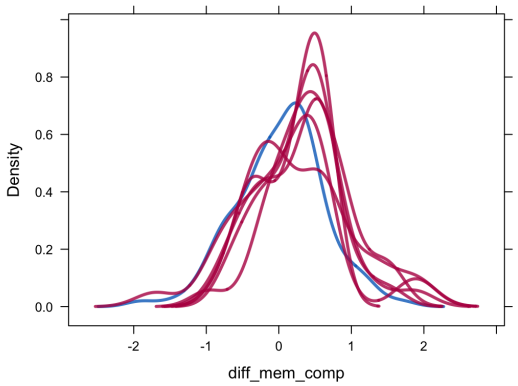
Figure 7: Density Plot of observed and imputed data



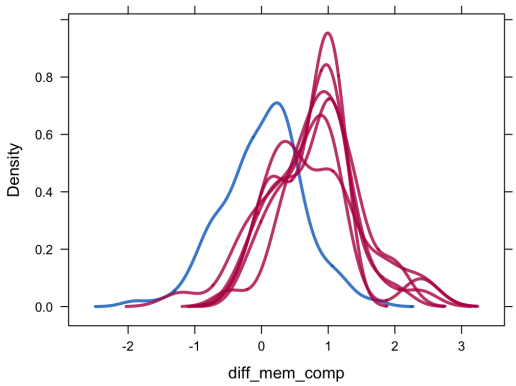
(a) $\delta = -0.7$



(b) $\delta = -0.2$

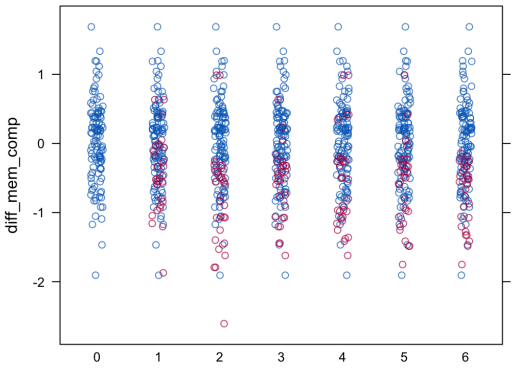


(c) $\delta = 0.2$

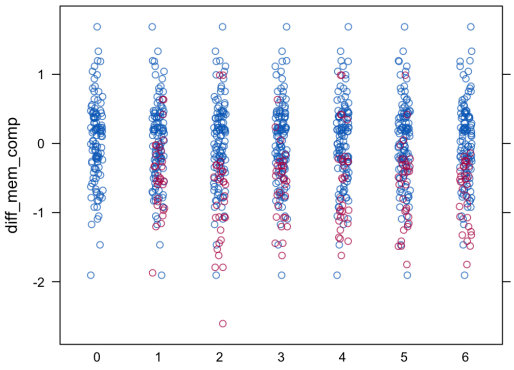


(d) $\delta = 0.7$

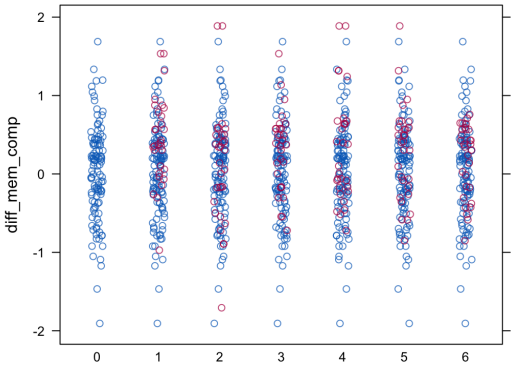
Figure 8: Stripplot of observed and imputed data



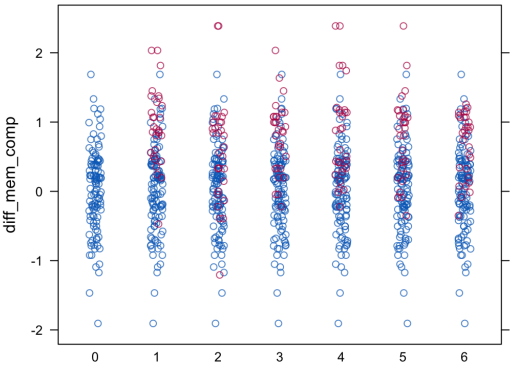
(a) $\delta = -0.7$



(b) $\delta = -0.2$



(c) $\delta = 0.2$



(d) $\delta = 0.7$

Table 7: $\delta = -0.7$ Summary Table

	term	estimate	std.error	statistic	df	p.value
1	(Intercept)	0.01	0.36	0.02	31.03	0.98
2	age	-0.01	0.01	-0.74	28.46	0.46
3	genderM	0.14	0.13	1.04	87.84	0.30
4	treatment_groupB	0.02	0.16	0.14	79.87	0.89
5	treatment_groupC	0.41	0.15	2.73	112.78	0.01
6	day19	-0.03	0.13	-0.26	65.37	0.80
7	day90	-0.24	0.13	-1.88	51.64	0.07

Table 8: $\delta = -0.2$ Summary Table

	term	estimate	std.error	statistic	df	p.value
1	(Intercept)	0.12	0.36	0.35	28.89	0.73
2	age	-0.01	0.01	-1.01	26.75	0.32
3	genderM	0.10	0.13	0.79	85.03	0.43
4	treatment_groupB	0.04	0.16	0.26	76.87	0.80
5	treatment_groupC	0.42	0.15	2.87	111.31	0.00
6	day19	0.07	0.11	0.66	51.69	0.51
7	day90	-0.09	0.12	-0.80	39.61	0.43

Table 9: $\delta = 0.2$ Summary Table

	term	estimate	std.error	statistic	df	p.value
1	(Intercept)	0.22	0.36	0.59	30.80	0.56
2	age	-0.01	0.01	-1.19	28.64	0.25
3	genderM	0.07	0.13	0.56	88.13	0.58
4	treatment_groupB	0.06	0.16	0.34	80.18	0.73
5	treatment_groupC	0.42	0.15	2.82	112.93	0.01
6	day19	0.16	0.11	1.45	49.60	0.15
7	day90	0.03	0.11	0.24	37.87	0.81

Table 10: $\delta = 0.7$ Summary Table

	term	estimate	std.error	statistic	df	p.value
1	(Intercept)	0.33	0.39	0.85	37.65	0.40
2	age	-0.01	0.01	-1.34	35.04	0.19
3	genderM	0.04	0.15	0.27	96.62	0.79
4	treatment_groupB	0.07	0.18	0.42	89.52	0.68
5	treatment_groupC	0.43	0.17	2.60	117.00	0.01
6	day19	0.27	0.12	2.24	59.17	0.03
7	day90	0.18	0.12	1.43	46.05	0.16

Table 11: Pooled Anova Test For Interaction Term

δ	statistic	df1	df2	p.value	riv
-0.7	0.99	4.00	234.45	0.41	0.32
-0.2	0.80	4.00	156.72	0.53	0.43
0.2	0.56	4.00	149.25	0.69	0.45
0.7	0.29	4.00	202.54	0.89	0.36