Effects of Dopamine-1 Receptor Agonist on Cognitive Deficits in Schizophrenia

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Background

- Cognitive deficits are common problems among individuals with schizophrenia (SCZ).
- To test whether stimulation of dopamine-1 receptors in the brain via a full, selective agonist (DAR-0100A) would improve cognitive deficits in schizophrenia.

Study Design

- Target population: 47 clinically stable individuals with SCZ.
- Treatments and control:
    - Group A: placebo (normal saline).
    - Group B: low dose (5mg) DAR-0100A.
    - Group C: high dose (15mg) DAR-0100A.
    - Individuals received drugs from Day 0 to Day 5 and from Day 15 to Day 19 (no drugs were administered from Day 5 to Day 15).
- Individuals were admitted to an inpatient clinic for a total of 19 days.
- Outcome measurements:
    - Composite memory score: the higher, the better.
    - Time of measurements: on Day 0, 5, 19, and 90.
- Baseline covariates: Age and gender.

Research Questions

- Treatment effects:
  - Treatment effects at days 5, 19, and 90.
  - Treatment effects differ over time.
- Sensitivity analyses: assessing the robustness of the missing data assumption.

EDA: Change of Memory Score Over Time

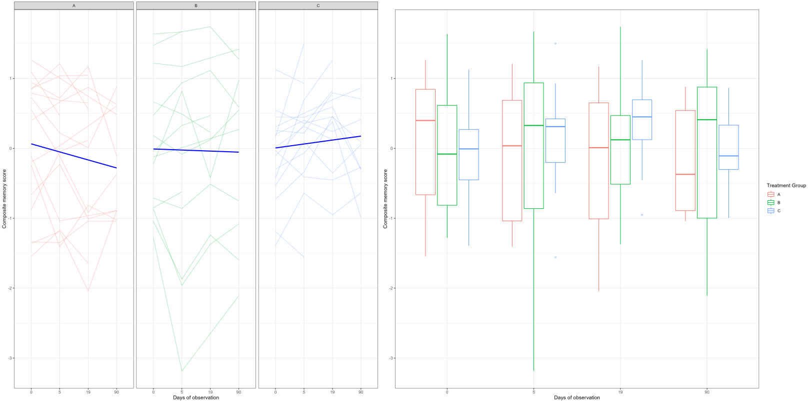

Figure: Change of memory score over time

EDA: Mean Memory Score for Completers and Dropouts

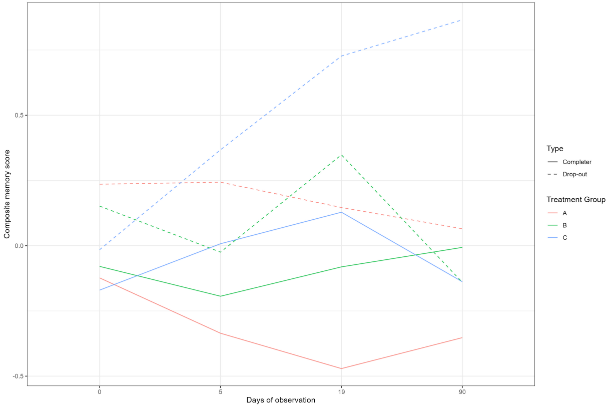

Figure: Change of memory score over time, completer vs dropouts

EDA: Proportion of Individuals that Stay in the Study

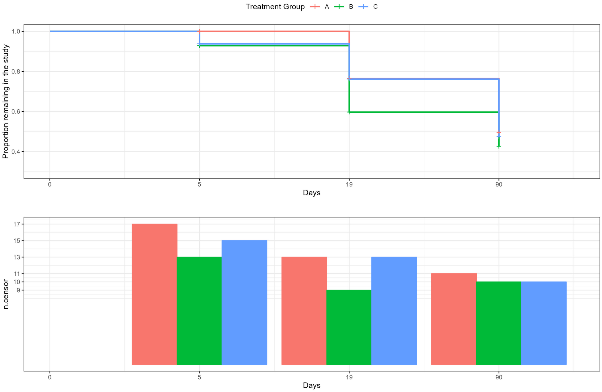

Figure: Proportion and numbers of individuals that stayed in the study

Statistical Analysis: Descriptive Statistics

	A	B	C	Overall
	(N=17)	(N=14)	(N=16)	(N=47)
Gender				
Female	9 (52.9%)	6 (42.9%)	7 (43.8%)	22 (46.8%)
Male	8 (47.1%)	8 (57.1%)	9 (56.3%)	25 (53.2%)
Age				
	40.35 (9.5)	37.57 (8.9)	39.50 (9.2)	39.23 (9.1)
Baseline Composite Memory Score				
	0.07 (0.9)	0.04 (1.0)	-0.10 (0.6)	0.00 (0.8)

Statistical Analysis: Setup

- Complete data for the k^{th} subject would consist of $n = 4$ measurements:

$$\boldsymbol{Y}_k = (Y_{k1}, Y_{k2}, \ldots, Y_{kn})^T$$
$$\boldsymbol{X}_k = (\boldsymbol{X}_{k1}, \boldsymbol{X}_{k2}, \ldots, \boldsymbol{X}_{kn})^T$$

  where $\boldsymbol{X}_{ki} = \left(X_{ki,1}, X_{ki,2}, \ldots, X_{ki,p}\right)$.
  - Including baseline age, gender, treatment group indicators, time variable (categorical), and the interaction between treatment and time.
- Define:

$$R_{ki} = \begin{cases} 1 & \text{if } Y_{ki} \text{ is observed} \\ 0 & \text{otherwise} \end{cases}$$

  and let $\boldsymbol{R}_k = (R_{k1}, \ldots, R_{kn})$.

Statistical Analysis: Model Setup

- Marginal model: $\mathrm{E}[Y_{ki} \mid \mathbf{X}_{ki}] = \mu_{ki} = \mathbf{X}_{ki}^T \beta$.
  $\boldsymbol{\mu}_k = (\mu_{k1}, \ldots, \mu_{kn})^T, n = 4$.
- More specifically,

$$
\begin{aligned}
\mathrm{E}[Y_{ki} \mid \mathbf{X}_{ki}] = \beta_0 &+ \beta_1 \cdot \mathbf{I}(t_{ki} = 5) + \beta_2 \cdot \mathbf{I}(t_{ki} = 19) \\
&+ \beta_3 \cdot \mathbf{I}(t_{ki} = 90) + \beta_4 \cdot \mathbf{I}(\text{treatment}_k = B) \\
&+ \beta_5 \cdot \mathbf{I}(\text{treatment}_k = C) + \beta_6 \cdot \text{age}_k \\
&+ \beta_7 \cdot \mathbf{I}(\text{gender}_k = \text{female}) \\
&+ \beta_9 \cdot \mathbf{I}(t_{ki} = 5) \cdot \mathbf{I}(\text{treatment}_k = B) \\
&+ \beta_{10} \cdot \mathbf{I}(t_{ki} = 19) \cdot \mathbf{I}(\text{treatment}_k = B) \\
&+ \beta_{11} \cdot \mathbf{I}(t_{ki} = 90) \cdot \mathbf{I}(\text{treatment}_k = B) \\
&+ \beta_{12} \cdot \mathbf{I}(t_{ki} = 5) \cdot \mathbf{I}(\text{treatment}_k = C) \\
&+ \beta_{13} \cdot \mathbf{I}(t_{ki} = 19) \cdot \mathbf{I}(\text{treatment}_k = C) \\
&+ \beta_{14} \cdot \mathbf{I}(t_{ki} = 90) \cdot \mathbf{I}(\text{treatment}_k = C)
\end{aligned}
$$

Statistical Analysis: Complete Case Analysis

- Assumption: Missing completely at random (MCAR)
- Restrict to those with $\boldsymbol{R}_k = \mathbf{1} = (1, \ldots, 1)$
- Complete-case GEE:

$$\sum_{k=1}^{K} I\left(\boldsymbol{R}_k = \mathbf{1}\right) \boldsymbol{D}_k^T \boldsymbol{V}_k^{-1} \left(\boldsymbol{Y}_k - \boldsymbol{\mu}_k\right) = \mathbf{0}$$

where $K = 47$.

  - $\boldsymbol{D}_k = \frac{\partial}{\partial \boldsymbol{\beta}} \boldsymbol{\mu}_k$.
  - $\boldsymbol{V}_k$: working covariance matrix.

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Statistical Analysis: Complete Case Analysis, Results

	Independent			AR-1			Exchangable		
Characteristics	Beta	95% CI	p-value	Beta	95% CI	p-value	Beta	95% CI	p-value
Days									
0	—	—		—	—		—	—	
5	-0.21	-0.56, 0.14	0.2	-0.21	-0.56, 0.14	0.2	-0.21	-0.56, 0.14	0.2
19	-0.35	-0.77, 0.07	0.11	-0.35	-0.77, 0.07	0.11	-0.35	-0.77, 0.07	0.11
90	-0.23	-0.62, 0.17	0.3	-0.23	-0.62, 0.17	0.3	-0.23	-0.62, 0.17	0.3
Treatment									
A	—	—		—	—		—	—	
B	0.06	-0.76, 0.88	0.9	0.08	-0.75, 0.90	0.9	0.06	-0.76, 0.88	0.9
C	-0.06	-0.76, 0.65	0.9	-0.05	-0.75, 0.65	0.9	-0.06	-0.76, 0.65	0.9
Age	0.00	-0.05, 0.05	>0.9	0.00	-0.04, 0.05	0.9	0.00	-0.05, 0.05	>0.9
Gender									
M	—	—		—	—		—	—	
F	-0.22	-0.94, 0.50	0.6	-0.18	-0.84, 0.48	0.6	-0.22	-0.94, 0.50	0.6
Days*Treatment									
5 * B	0.10	-0.51, 0.71	0.8	0.10	-0.51, 0.71	0.8	0.10	-0.51, 0.71	0.8
19 * B	0.35	-0.15, 0.84	0.2	0.35	-0.15, 0.84	0.2	0.35	-0.15, 0.84	0.2
90 * B	0.30	-0.26, 0.86	0.3	0.30	-0.26, 0.86	0.3	0.30	-0.26, 0.86	0.3
5 * C	0.39	-0.03, 0.81	0.067	0.39	-0.03, 0.81	0.067	0.39	-0.03, 0.81	0.067
19 * C	0.65	0.13, 1.2	0.014	0.65	0.13, 1.2	0.014	0.65	0.13, 1.2	0.014
90 * C	0.26	-0.27, 0.79	0.3	0.26	-0.27, 0.79	0.3	0.26	-0.27, 0.79	0.3

Statistical Analysis: IPW Available Data Analysis

- Assumption: Missing at random (MAR)
- Consider the following IPW available-data GEE:

$$\sum_{k=1}^{K} \boldsymbol{D}_k^T \boldsymbol{V}_k^{-1} \boldsymbol{\Delta}_k \left(\boldsymbol{Y}_k - \boldsymbol{\mu}_k \right) = \mathbf{0}$$

  where $\Delta_k = \mathcal{R}_k \mathcal{W}_k$ weighting matrix.
  - $\mathcal{R}_k$ is an $n \times n$ diagonal matrix with elements $\mathbf{I}\left(R_{ki} = 1\right)$ on the diagonal indicating whether or not the i^{th} measurement is observed.
  - $\mathcal{W}_k$ is an $n \times n$ diagonal matrix with elements π_{ki}^{-1} on the diagonal.
- Let $\lambda_{ki} = P(R_{ki} = 0 \mid R_{ki-1} = 1, \mathbf{X}_{ki})$, the hazard of drop-out. We used the proportional hazard model to model it.
  - Interpret π_{ki} as the survival probability.

Statistical Analysis: Propensity Score Model Result

Characteristics	HR	95% CI	p-value
Treatment			
A	—	—	
B	1.22	0.50, 2.96	0.7
C	1.09	0.45, 2.63	0.8
Age	0.97	0.94, 1.02	0.2
Gender			
M	—	—	
F	1.47	0.70, 3.08	0.3

Statistical Analysis: Model Results

	Independent			AR-1			Exchangable		
Characteristics	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Days									
0	—	—		—	—		—	—	
5	-0.10	-0.35, 0.15	0.4	-0.10	-0.35, 0.15	0.4	-0.10	-0.34, 0.15	0.4
19	-0.29	-0.66, 0.07	0.12	-0.24	-0.59, 0.10	0.2	-0.22	-0.54, 0.09	0.2
90	-0.32	-0.75, 0.11	0.14	-0.14	-0.51, 0.23	0.5	-0.19	-0.53, 0.15	0.3
Treatment									
A	—	—		—	—		—	—	
B	-0.07	-0.72, 0.58	0.8	-0.10	-0.75, 0.55	0.8	-0.11	-0.76, 0.54	0.7
C	-0.18	-0.71, 0.35	0.5	-0.17	-0.70, 0.35	0.5	-0.22	-0.74, 0.31	0.4
Age	-0.01	-0.05, 0.02	0.5	-0.01	-0.05, 0.02	0.4	-0.02	-0.06, 0.02	0.4
Gender									
M	—	—		—	—		—	—	
F	-0.05	-0.61, 0.52	0.9	0.06	-0.47, 0.60	0.8	-0.01	-0.61, 0.59	>0.9
Days*Treatment									
5 * B	-0.05	-0.53, 0.43	0.8	-0.05	-0.50, 0.41	0.8	-0.05	-0.51, 0.41	0.8
19 * B	0.22	-0.36, 0.80	0.4	0.25	-0.21, 0.70	0.3	0.19	-0.23, 0.60	0.4
90 * B	0.25	-0.39, 0.89	0.4	0.26	-0.21, 0.73	0.3	0.23	-0.24, 0.70	0.3
5 * C	0.36	0.00, 0.71	0.050	0.38	0.03, 0.72	0.031	0.39	0.04, 0.74	0.027
19 * C	0.74	0.25, 1.2	0.003	0.70	0.25, 1.1	0.002	0.68	0.25, 1.1	0.002
90 * C	0.40	-0.19, 0.99	0.2	0.31	-0.24, 0.85	0.3	0.32	-0.18, 0.81	0.2

EDA: Missing Data

Variable		Observed %	Missing %
Day	P-value<0.001		
0		30	0
5		28	7
19		22	40
90		20	53

EDA: Missing Data

Variable		Observed %	Missing %
Gender	P-value=0.238		
M		55	43
F		45	57

EDA: Missing Data

Variable		Observed %	Missing %
Treatment Group	P-value=0.889		
A		37	33
B		29	33
C		34	33

MAR: GEE with Multiple Imputation

term	estimate	std.error	p.value
(Intercept)	0.7144858	0.7027786	0.3108280
day 5	-0.0957728	0.1263164	0.4493703
day 19	-0.3426499	0.2460425	0.1711387
day 90	-0.2207704	0.3169249	0.4962279
treatment B	-0.0775200	0.3307685	0.8149819
treatment C	-0.1858332	0.2703099	0.4927058
age	-0.0155721	0.0151565	0.3057402
genderF	-0.0366938	0.2607142	0.8883354
day 19:treatment C	0.7252705	0.3025770	0.0185939

Table: GEE Output with Multiple Imputation

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EDA: Missing Data

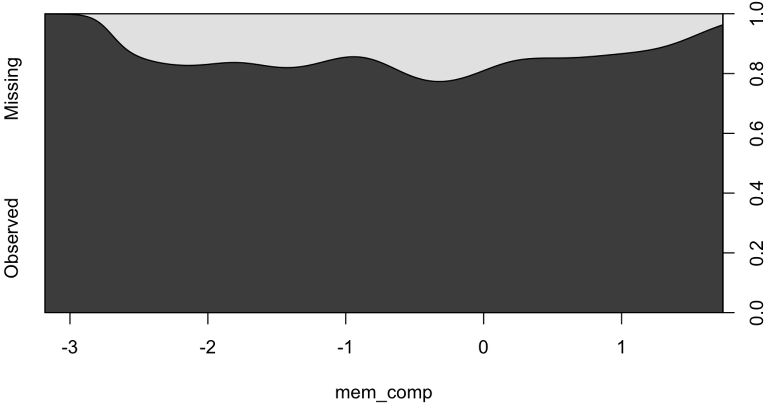

Figure: Probability of Missing Data Conditional on Outcome (MAR)

MNAR: Sensitivity Analysis

- The imputations created are based on the assumption that the data are MAR, which may not be true
- We want to leverage the sensitivity analysis is to explore the result of the analysis under alternative scenarios for the missing data
- We propose to use the delta-adjustment method that can account for accounts for shift bias, scale bias and shape bias

MNAR: Sensitivity Analysis Cont.

δ	estimate	std.error	p.value
-0.4	0.744	0.322	2.29E-02
-0.3	0.74	0.316	2.15E-02
-0.2	0.735	0.311	2.03E-02
-0.1	0.73	0.307	1.93E-02
0	0.725	0.303	1.86E-02
0.1	0.72	0.299	1.81E-02
0.2	0.716	0.296	1.78E-02
0.3	0.711	0.294	1.78E-02
0.4	0.706	0.293	1.80E-02

Table: Perform δ-adjustment on $\beta_{day19:treatmentC}$

Conclusions

- Treatment effect:
  - No significant treatment effect was found in both analyses.
  - Significant interactions were found between treatment C and time.
- Sensitivity analysis:
  - Though the imputations differ dramatically under the various scenarios, the beta estimates for different δ are close. Thus, the results are essentially the same under all specified MNAR mechanisms.

Reference

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