Modeling Persistent Cognitive Deficits in a Mouse Model of Schizophrenia: Role of Phencyclidine (PCP) Dosing Frequency and Reversal by Clinically Relevant Compounds

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Background / Objective

- **Schizophrenia** is a severe psychiatric disorder involving positive, negative, and cognitive symptoms. Cognitive impairments are a core feature, often appearing early and persisting throughout the illness. Critically, they are strongly linked to poor functional outcomes and remain largely unresponsive to current antipsychotic treatments.
- This study aimed to develop a translational mouse model of schizophrenia-related cognitive impairment using repeated administration of **phencyclidine** (PCP), an NMDA receptor antagonist. The goal was to induce persistent deficits that could be reversed by clinically relevant pro-cognitive agents, supporting the model's use in therapeutic screening.

Material and Methods

Male CD-1 mice were used.

- PCP administered in varying doses (0.2–10 mg/kg) and frequencies (q.d. vs. b.i.d.),
- T-maze spontaneous alternation task used to assess cognition at 30 minutes, 1 day or 3 days PCP post-withdrawal,
- Travelled distance in the Open Field (60 minutes) and immobility time in the Forced Swimming test are used to measure hyperactivity and behavioral dispair, respectively,
- Acute administration of **Vortioxetine** and **Modafinil** tested for reversal of cognitive deficits.

Results

Table **1** : Search for an effective PCP regimen to induce acute and persistent cognitive deficits in mice

Consecutive Treatment days	Dosing frequency	Dose of PCP (mg/kg)	Cumulative dose of PCP (mg/kg)	Timepoint for Spontaneous Alternation assay	PCP Group (% Alternation ± SEM)	Vehicle Group (% Alternation ± SEM)	Significant?	Interpretation
1	q.d.	1	1	30 min post-withdrawal	57 ± 5	73 ± 3	No	No acute effect
1	q.d.	3	3	30 min post-withdrawal	39 ± 2	64 ± 2	Yes	Acute deficit
10	q.d.	1	10	30 min post-withdrawal	51 ± 6	71 ± 4	No	No acute effect
10	q.d.	3	30	30 min post-withdrawal	41 ± 2	72 ± 3	Yes	Acute deficit
10	q.d.	3	30	1 day post-withdrawal	62 ± 6	71 ± 3	No	No persistant effect
10	q.d.	5	50	1 day post-withdrawal	61 ± 4	71 ± 3	No	No persistant effect
10	q.d.	10	100	1 day post-withdrawal	66 ± 5	68 ± 3	No	No persistant effect
10	q.d.	10	100	3 days post-withdrawal	61 ± 5	71 ± 3	No	No persistant effect
8	b.i.d.	0.2	3.2	3 days post-withdrawal	53 ± 3	70 ± 2	Yes	Persistant effect
12	b.i.d.	0.2	4.8	3 days post-withdrawal	36 ± 3	66 ± 2	Yes	Persistant effect
12	b.i.d.	2	48	3 days post-withdrawal	46 ± 3	69 ± 2	Yes	Persistant effect

Table **2** : Reversal effect of Vortioxetine and Modafinil on PCP-induced persistent cognitive deficits in mice

Group Nr.	Groups description	n	Spontaneous Alternation (%)	s.e.m.	% Reversion	Significant vs Gr. Nr. 2?	Interpretation
1	Saline / Vehicle	9	68	2	100	Yes	Unaltered cognitive function
2	PCP 0.2 mg/kg;b.i.d. / Vehicle	10	44	3	0	No	Persistent cognitive deficit
3	PCP 0.2 mg/kg;b.i.d. / Vortioxetine 1 mg/kg	10	54	3	39	No	Dose-dependent reversion of the cognitive deficit
4	PCP 0.2 mg/kg;b.i.d. / Vortioxetine 3 mg/kg	10	58	5	57	No	
5	PCP 0.2 mg/kg;b.i.d. / Vortioxetine 10 mg/kg	10	61	4	69	Yes	
6	PCP 0.2 mg/kg;b.i.d. / Modafinil 3 mg/kg	10	54	3	42	No	Dose-dependent reversion of the cognitive deficit
7	PCP 0.2 mg/kg;b.i.d. / Modafinil 10 mg/kg	10	57	4	54	No	
8	PCP 0.2 mg/kg;b.i.d. / Modafinil 30 mg/kg	10	64	5	80	Yes	

Results (continued)

Table **3** : No effect of Vortioxetine or Modafinil on acute PCP-induced hyperlocomotion in mice

Group Nr.	Groups description	n	**Travelled distance** during the 25 min pretreatment (PCP-free period)		Significant vs Gr. Nr. 2?	**Travelled distance** during the 60 min post-PCP challenge		Significant vs Gr. Nr. 2?
			Mean	s.e.m.		Mean	s.e.m.	
1	Vehicle/Saline	8	8978	590	No	13390	1152	Yes
2	Vehicle / PCP 3 mg/kg	8	8762	435	No	37015	4099	No
3	Vortioxetine 1 mg/kg / PCP 3 mg/kg	9	9046	309	No	30027	4057	No
4	Vortioxetine 3 mg/kg / PCP 3 mg/kg	9	10331	697	No	29035	2530	No
5	Vortioxetine 10 mg/kg / PCP 3 mg/kg	9	9517	835	No	34011	2985	No
6	Modafinil 3 mg/kg / PCP 3 mg/kg	9	9204	755	No	30594	3732	No
7	Modafinil 10 mg/kg / PCP 3 mg/kg	9	10535	903	No	35560	1777	No
8	Modafinil 30 mg/kg / PCP 3 mg/kg	9	11845	745	Yes	36485	1908	No

Table **4** : No effect of Vortioxetine or Modafinil on Forced Swimming-induced behavioral despair in mice

Group Nr.	Groups description	n	**Immobility time** during the Forced swim test		Significant vs Gr. Nr. 1?
			Mean	s.e.m.	
1	Vehicle	10	187	7	No
2	Vortioxetine (1 mg/kg, s.c., 60 min)	10	193	13	No
3	Vortioxetine (3 mg/kg, s.c., 60 min)	10	190	10	No
4	Vortioxetine (10 mg/kg, s.c., 60 min)	10	192	12	No
5	Modafinil (3 mg/kg,p.o., 30 min)	10	206	6	No
6	Modafinil (10 mg/kg,p.o., 30 min)	10	194	9	No
7	Modafinil (30 mg/kg,p.o., 30 min)	10	171	11	No

Keypoints

- Acute cognitive deficits observed only at ≥ 3 mg/kg,
- q.d. dosing up to 10 mg/kg over 10 days did not induce persistent impairment,
- b.i.d. low-dose (0.2 mg/kg) over 8–12 days caused persistent deficits up to 3 days post-withdrawal,
- Higher b.i.d. dose (2 mg/kg) did not increase severity of deficit,
- **Vortioxetine** and **Modafinil** reversed deficits without affecting hyperlocomotion or despair.

Conclusion

- This model reflects persistent schizophrenia-like cognitive impairments,
- Deficits persist far beyond PCP's half-life (~ 2-3 hours), suggesting neurobiological changes,
- Reversal by **Vortioxetine** and **Modafinil** supports model's translational validity,
- Enables screening of novel cognitive therapies targeting long-lasting cognitive dysfunction.