Functional MRI evidence for dopaminergic neuromodulation of semantic priming in healthy individuals

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Introduction

The role of dopamine (DA) in cognition has been largely conceptualised in terms of working memory and cognitive control, yet there is emerging evidence that dopamine can influence aspects of semantic processing.

Semantic priming is modulated on versus off Levodopa (L-Dopa) in Parkinson's Disease (Murdoch et al.,) and on versus off neuroleptics in schizophrenia (Goldberg et al., 2000).

Ingestion of L-Dopa in healthy individuals reduces indirect semantic priming (Kischka et al., 1996, see also Angwin et al., 2004). which may reflect a DA role in increasing focus and reducing spreading activation in semantic networks.

Kischka et al. (1996) speculated that L-Dopa probably modulates semantic priming through mesocortical projections, yet the neural mechanisms involved have not been investigated.

The present study investigated whether the proposed cognitive role of DA in selecting from competing representations includes the frequency-based selection of ambiguous word meanings (e.g. bank-money, bank-river) and sought to determine the neural basis of this modulation.

Aims

This study aimed to determine the brain regions involved in the dopaminergic modulation of semantics in healthy individuals by combining pharmacological event-related fMRI with a lexical ambiguity semantic priming task.

Method

SUBJECTS

20 right handed healthy participants (8 female; mean age = 25 years).

STUDY DESIGN

A double-blind placebo controlled crossover design was employed. Subjects were randomly assigned to placebo or levodopa (capsule containing 100 mg levodopa and 25 mg benserazide) sessions and received the other treatment approximately 1 week later.

PRIMING TASK

150 randomly presented ambiguity prime-target word pairs (30 dominant related (e.g. bank-money), 30 subordinate related (e.g. bank-river), 30 unrelated, 60 nonword) with interstimulus interval (ISI) of 150 ms. Subjects made speeded lexical decisions (word/nonword) on targets using dual response procedure. The task was performed approximately 45 minutes after ingestion.

IMAGE ACQUISITION

Images were acquired using a 4T Bruker MedSpec. 570 EPI images were acquired over 2 runs (TE 30ms, TR 2100ms). Each brain volume consisted of 36 planes, in-plane resolution 3.6mm and slice thickness 3mm (0.6mm gap). A high-resolution MP-RAGE 3D T_1 image was acquired within the same session (TI 1500ms, TR 2500ms, TE 3.83ms, resolution 0.9 x 0.9 x 0.9mm).

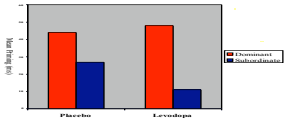
IMAGE ANALYSIS

- Data were slice-timing corrected, spatially normalised via non-linear basis function to T1 and EPI template images in SPM2, and smoothed (FWHM 8 mm Gaussian).
- Fixed-effects model applied to signal intensity time-course of each voxel including covariates consisting of synthetic haemodynamic response function & temporal derivative for transient BOLD responses for 5 trial types (dom, sub, unr, non, errors).
- Within subject analyses were performed to define priming and drug only plus drug x priming interactions.
- Contrast images were entered into one tailed t-test in a group random effects analysis. Voxels exceeding p < .001 (uncorrected) with a minimum cluster of 5 voxels are reported.

Results

Blood pressure, heart rate, and subject mood ratings did not differ between the L-Dopa and Placebo sessions.

BEHAVIOURAL RESULTS



Linear Mixed Model analyses on lexical decision latencies revealed a main effect of condition (F (2, 3513) = 61.718, p <.0001), and a drug x condition interaction (F (2, 3513) = 3.512, p = .030) indicating reduced subordinate priming on L-Dopa.

DOMINANT VERSUS UNRELATED

Region	Z score	Coordinates			
		x	y	z	P (unc)
Drug Main Effect					
(L-Dopa<Placebo)					
L Precuneus	4.25	-15	-63	63	0.000
Left STG	3.69	-60	-45	12	0.000
L SFG	3.68	-15	30	45	0.000
L Lingual Gyrus	3.60	-24	-66	-3	0.000
R MTG	3.53	45	-51	12	0.000
L Supramarginal	3.43	-45	-39	24	0.000
R SMA	3.37	9	9	60	0.000
Drug X Condition Interaction					
Right ACC	3.88	9	42	9	0.000
Right STG	3.87	60	-21	6	0.000
Left Putamen	3.56	-15	6	-9	0.000
R Precuneus	3.31	9	-48	57	0.000

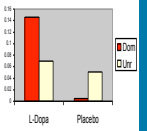


Figure 2. Mean % Signal change in Right ACC

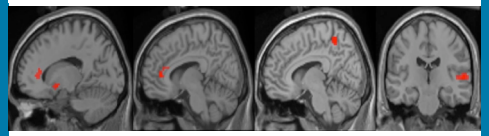


Figure 3. Regions showing a significant drug x condition (dominant, unrelated) interaction

SUBORDINATE VERSUS UNRELATED

Region	Z score	Coordinates			
		x	y	z	p (unc)
Drug Main Effect					
(L-Dopa<Placebo)					
L Precuneus	4.41	-15	-63	63	0.000
R Postcentral Gyrus	3.64	27	-30	63	0.000
L Lingual Gyrus	3.63	-21	-69	-6	0.000
L STG	3.57	-60	-45	12	0.000
R MTG	3.47	42	-51	15	0.000
L Supramarginal G	3.39	-45	-39	24	0.000
R Hippocampus	3.34	30	-27	-6	0.000
(L-Dopa>Placebo)					
R Cerebellum	3.73	33	-72	-27	0.000
R Precuneus	3.66	21	-45	3	0.000
Drug X Condition Int					
R Thalamus	4.21	21	-18	6	0.000
L Thalamus	3.66	-21	-33	15	0.000

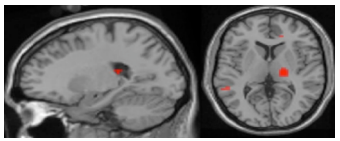


Figure 4. Regions showing a significant drug x condition (subordinate, unrelated) interaction

DOMINANT VERSUS SUBORDINATE

Region	Z score	Coordinates			
		x	y	z	p (unc)
Drug Main Effect					
(L-Dopa<Placebo)					
L Precuneus	4.53	-15	-63	63	0.000
L Lingual Gyrus	3.75	-24	-69	-3	0.000
R MTG	3.69	45	-51	15	0.000
L Supramarginal Gyrus	3.47	-45	-39	24	0.000
L SFG	3.39	-15	30	45	0.000
(L-Dopa>Placebo)					
R Precuneus	4.18	21	-45	3	0.000
R STG	3.65	60	-27	0	0.000
R Cerebellum	3.64	33	-72	-27	0.000
Drug X Condition Int					
L Middle Cingulate	3.92	-9	-24	42	0.000
R SMA	3.81	3	-24	51	0.000

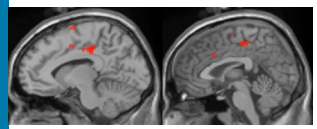


Figure 5. Regions showing a significant drug x condition (dominant, subordinate) interaction

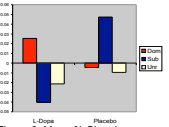


Figure 6. Mean % Signal change in Left Middle Cingulate

Conclusion

L-Dopa did not affect behavioural dominant priming, however, the associated pattern of brain activity was consistent with repetition suppression on placebo (reduced BOLD signal for primed targets) but response enhancement (increased signal for primed targets) on L-Dopa. This may be consistent with enhanced DA-based signaling during meaning activation.

Reduced priming of subordinate meanings on L-Dopa is also consistent with a DA role in enhancing semantic salience by reducing activation for competing weaker representations, as further demonstrated by reduced BOLD signal in the left cingulate for subordinate meanings versus dominant meanings on L-Dopa.

Within a lexical decision priming paradigm, L-Dopa appeared to enhance frequency based selective meaning activation via mesocorticolimbic and nigrostriatal systems, which is consistent with findings of disturbed meaning selection in PD (Copland, 2003).

References

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