FIG. 1A.

OxyAs DNAts OxyTs DNAcs DNAcs DNAts DNAts DNAas DNAcs DNAas DNAcs DNAcs OxyAs OxyMCs OxyAs OxyMC

FIG. 1B.

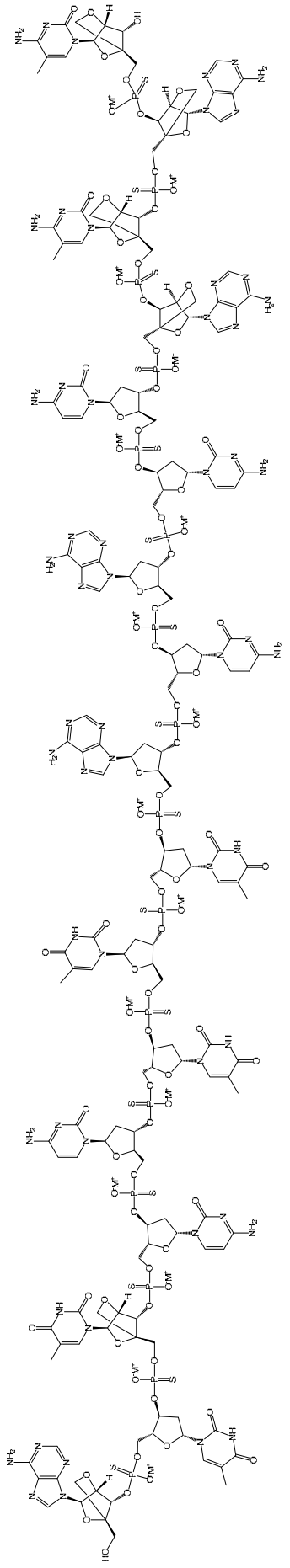


FIG. 2B

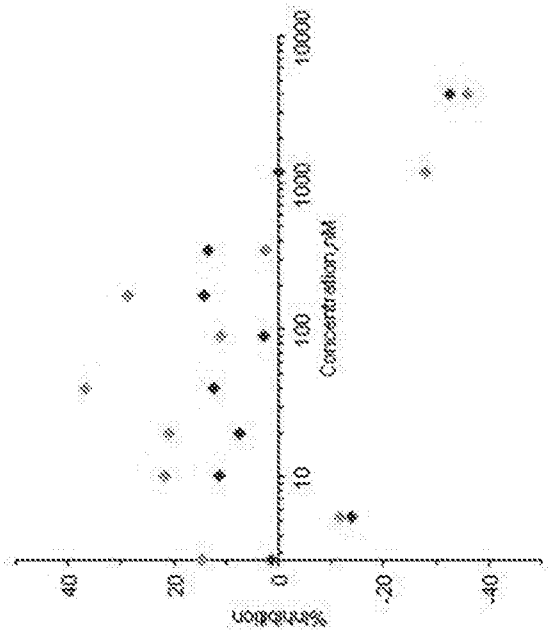
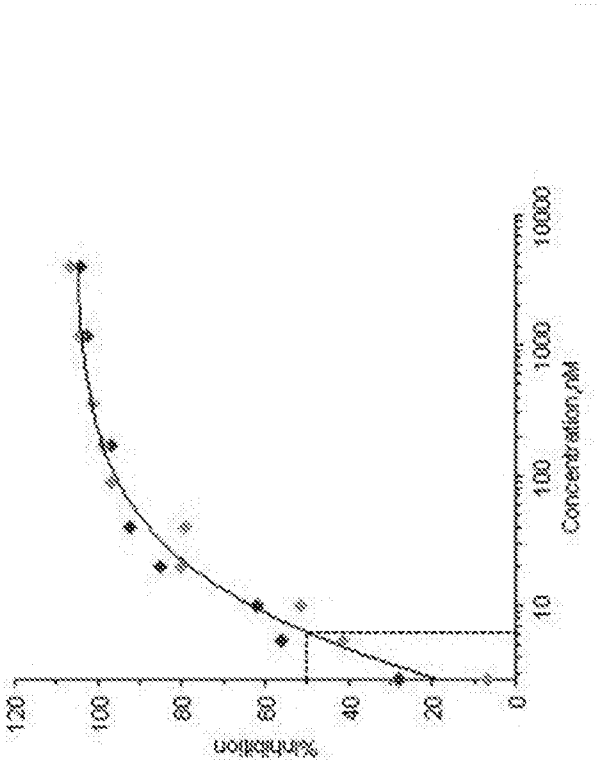

Tub
% Inhibition
Concentration, nM
40
20
0
-20
-40
10
100
1000
10000

FIG. 2A


aSyn/Tub
% Inhibition
Concentration, nM
120
100
80
60
40
20
0
10
100
1000
10000

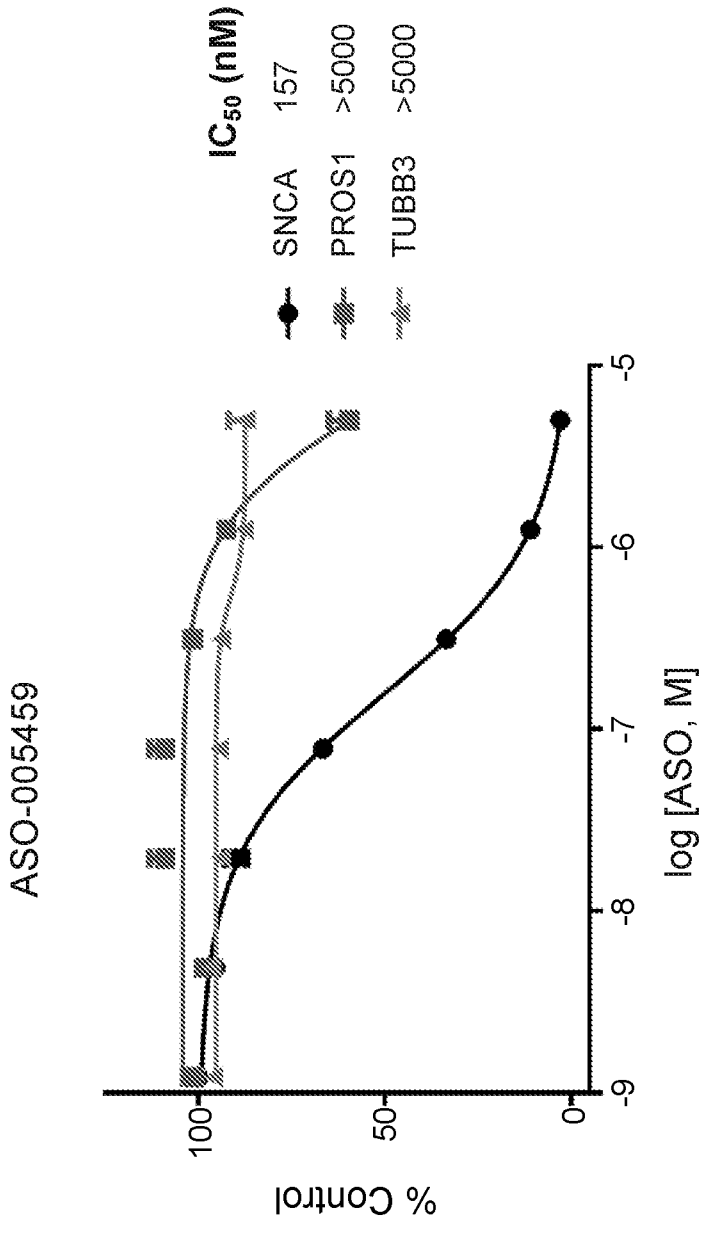

ASO-005459
IC50 (nM)
SNCA 157
PROS1 >5000
TUBB3 >5000
% Control
100
50
0
-5
-6
-7
-8
-9
log [ASO, M]

FIG. 3

FIG. 4

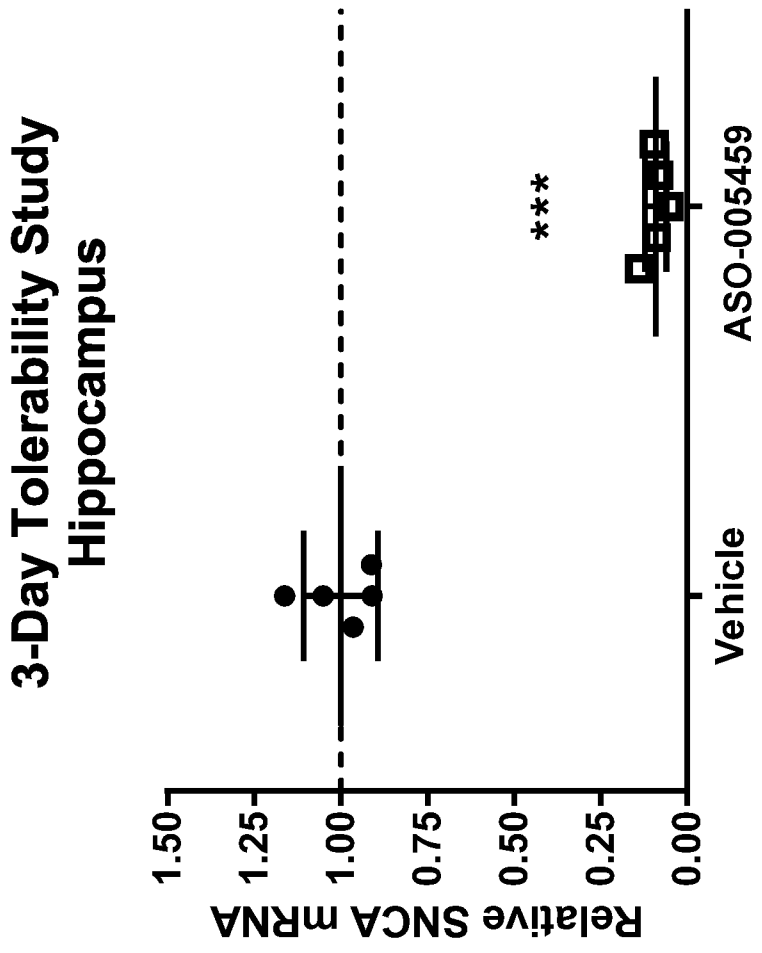
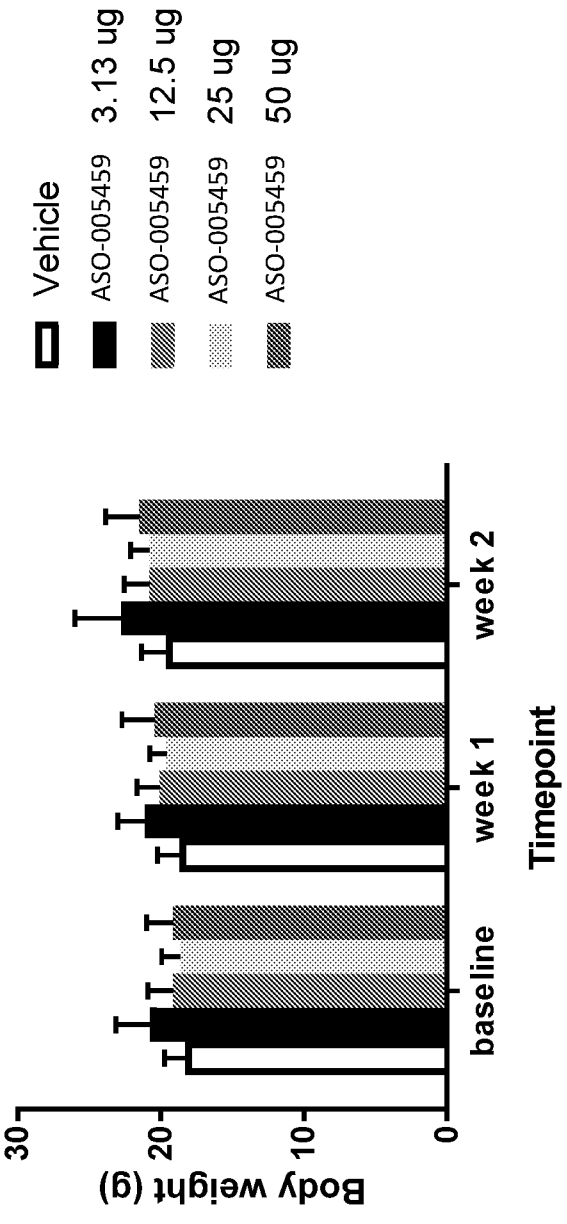

3-Day Tolerability Study
Hippocampus
Relative SNCA mRNA
1.50
1.25
1.00
0.75
0.50
0.25
0.00
***
Vehicle
ASO-005459

FIG. 5A


14-Day Dose Response Study
Body weight
Vehicle
ASO-005459 3.13 ug
ASO-005459 12.5 ug
ASO-005459 25 ug
ASO-005459 50 ug
Body weight (g)
30
20
10
0
baseline
week 1
week 2
Timepoint

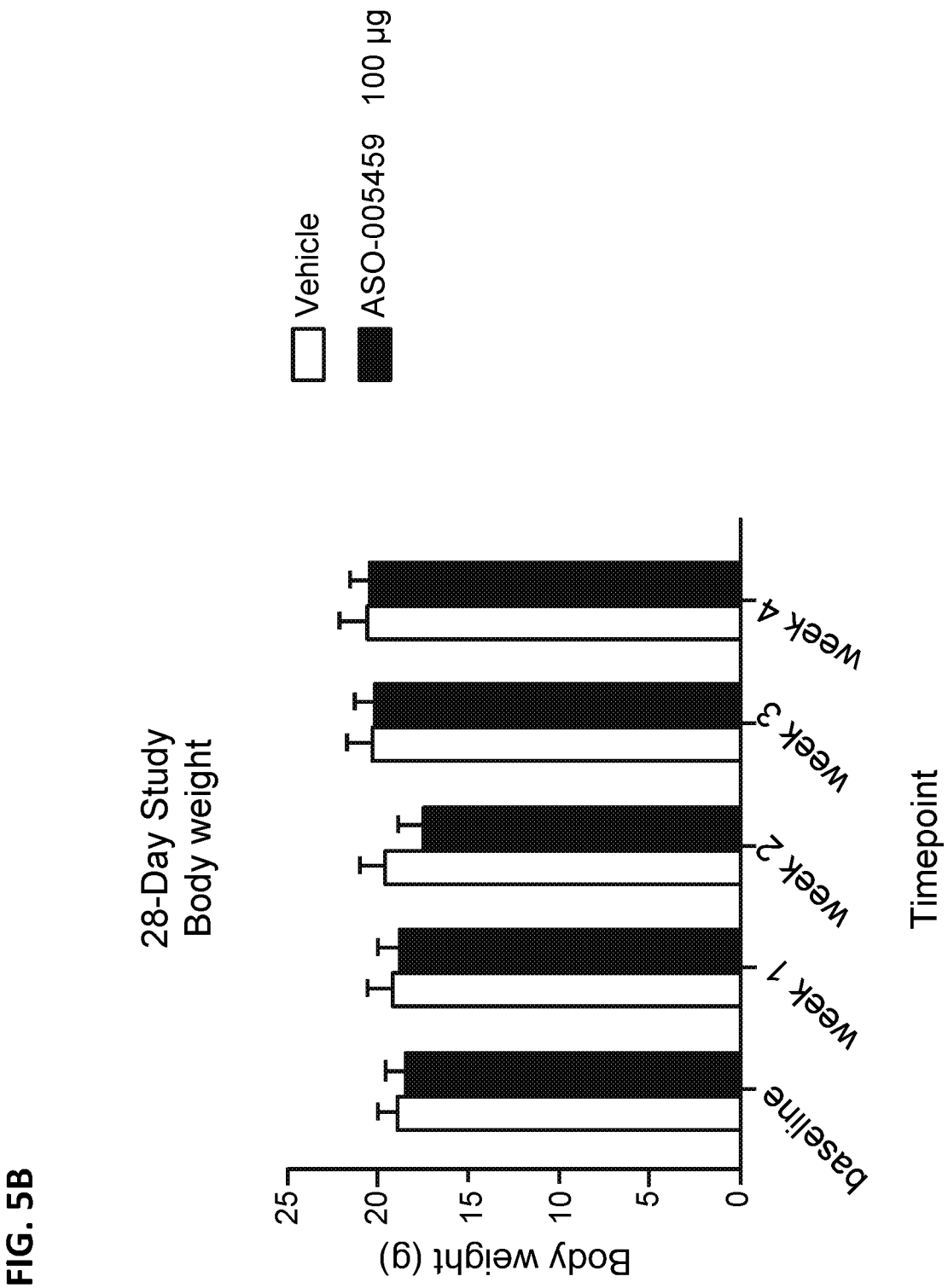

28-Day Study
Body weight
Vehicle
ASO-005459 100 µg
Body weight (g)
0
5
10
15
20
25
baseline
week 1
week 2
week 3
week 4
Timepoint

FIG. 5B

FIG. 6A

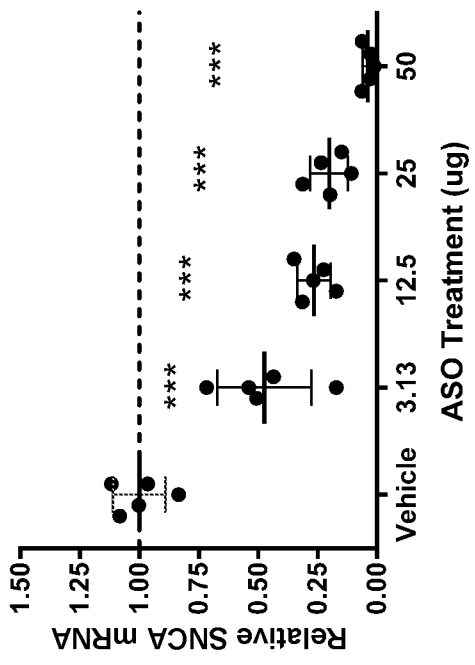


FIG. 6B

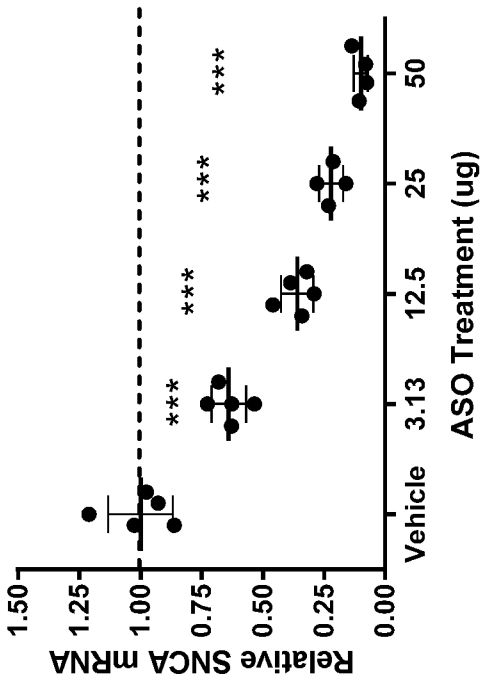
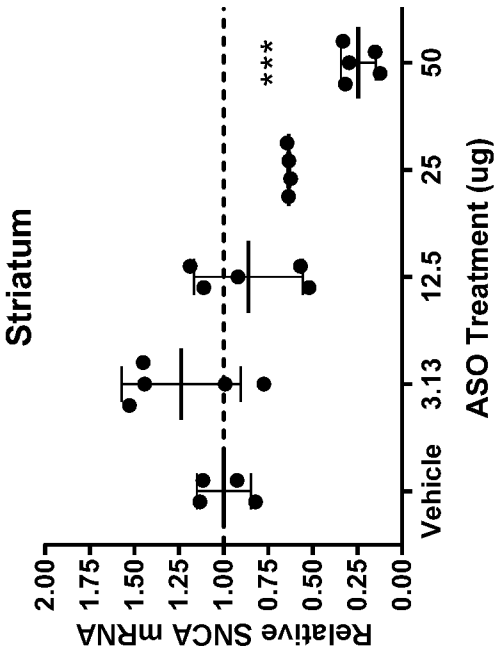


FIG. 6C



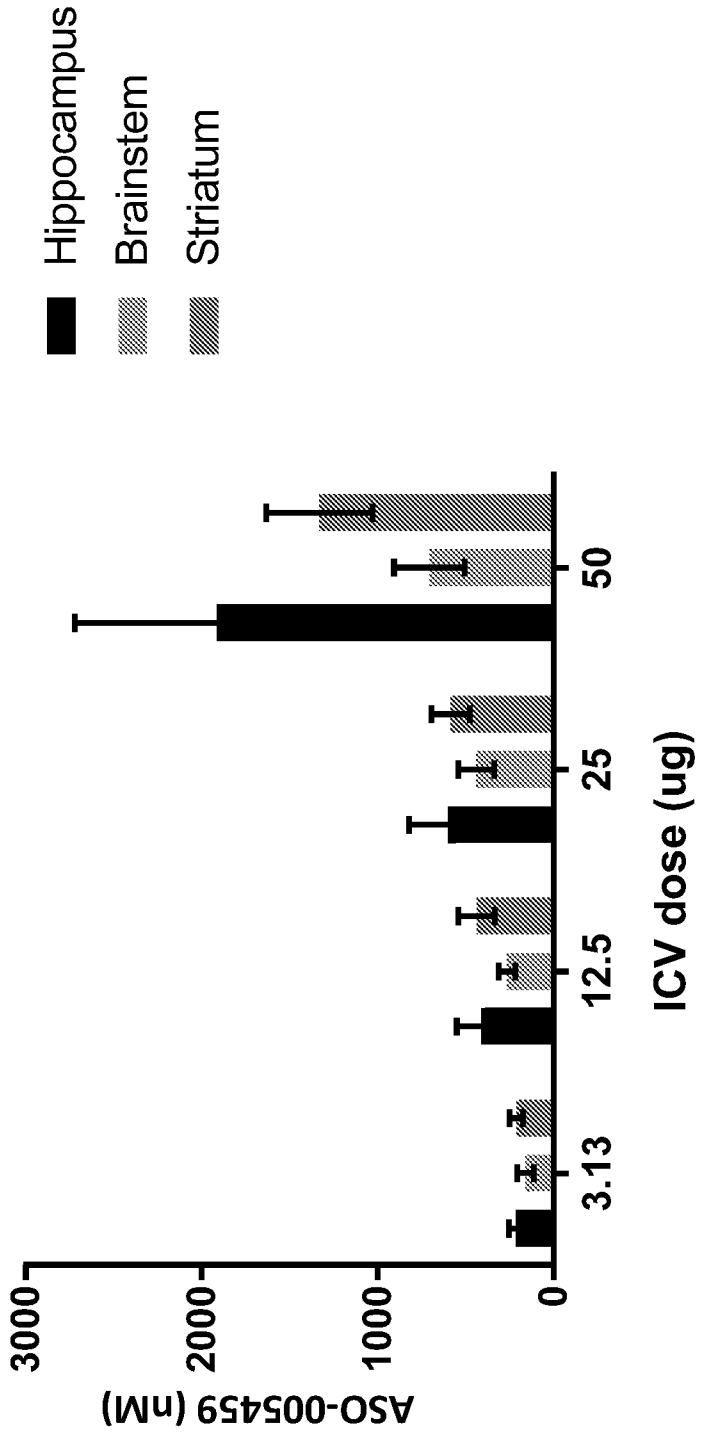

Hippocampus
Brainstem
Striatum
ASO-005459 (nM)
3000
2000
1000
0
3.13
12.5
25
50
ICV dose (ug)

FIG. 7

FIG. 8A

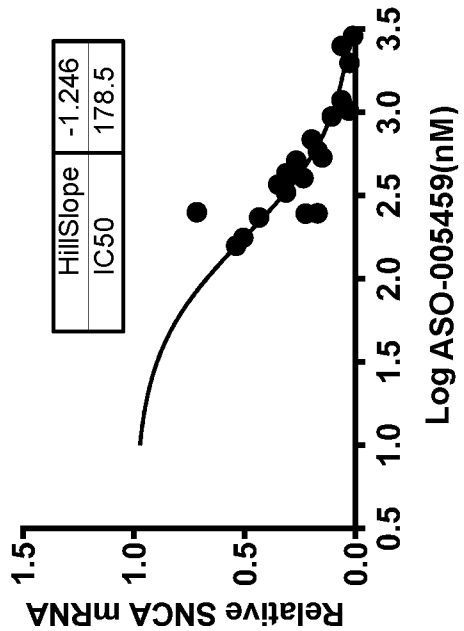


FIG. 8B

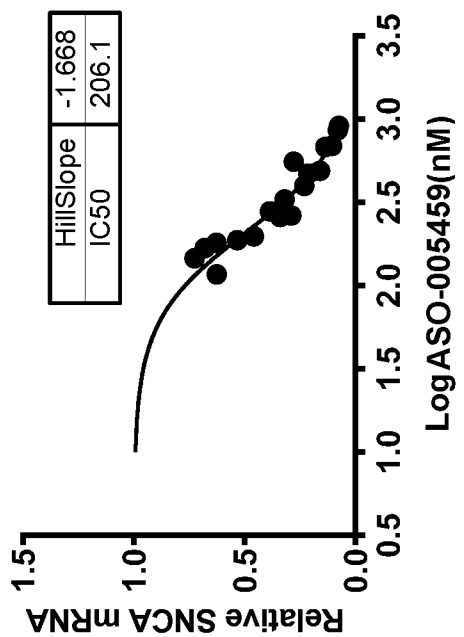


FIG. 8C

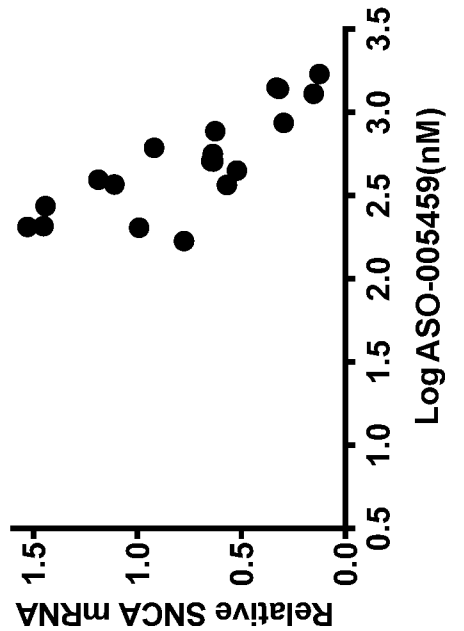
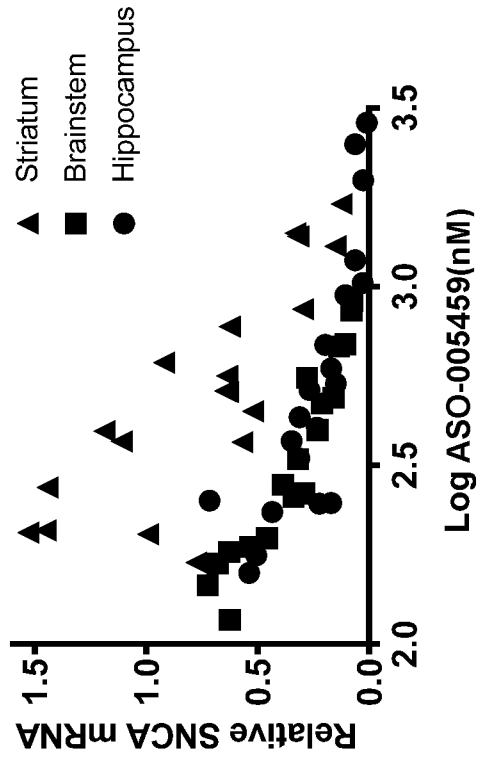


FIG. 8D



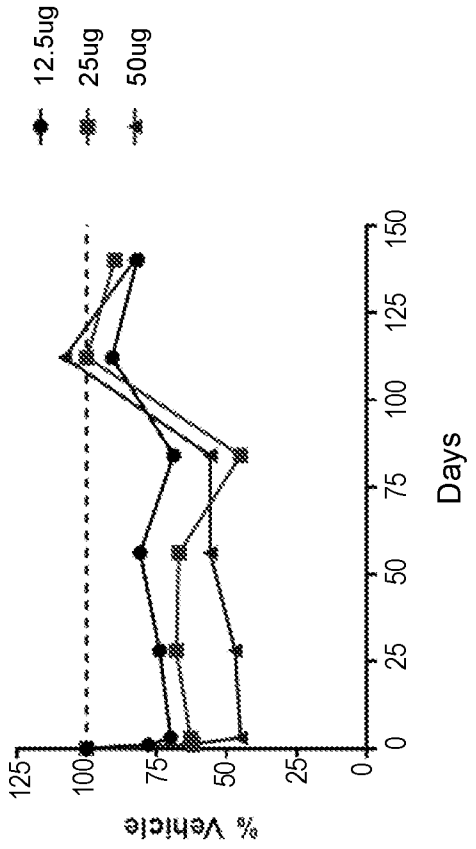

mRNA Reduction
Striatum Summary
12.5ug
25ug
50ug
% Vehicle
125
100
75
50
25
0
0
25
50
75
100
125
150
Days

FIG. 9B

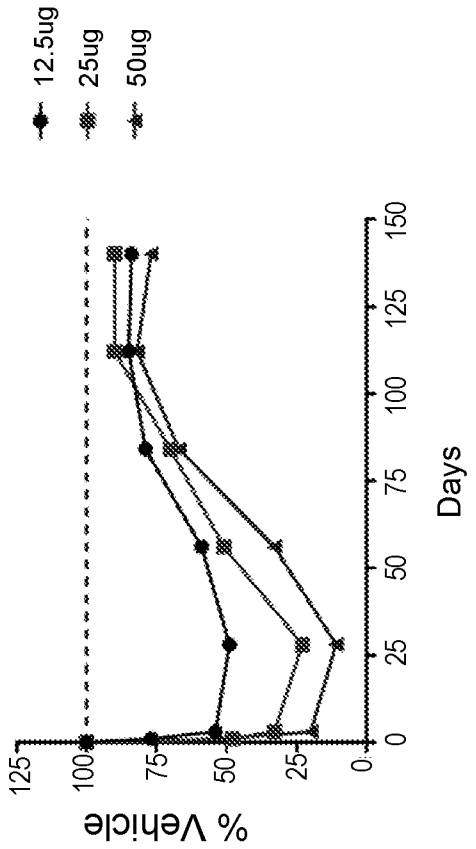

mRNA Reduction
Brain Stem Summary
12.5ug
25ug
50ug
% Vehicle
125
100
75
50
25
0
0
25
50
75
100
125
150
Days

FIG. 9A

FIG. 10A

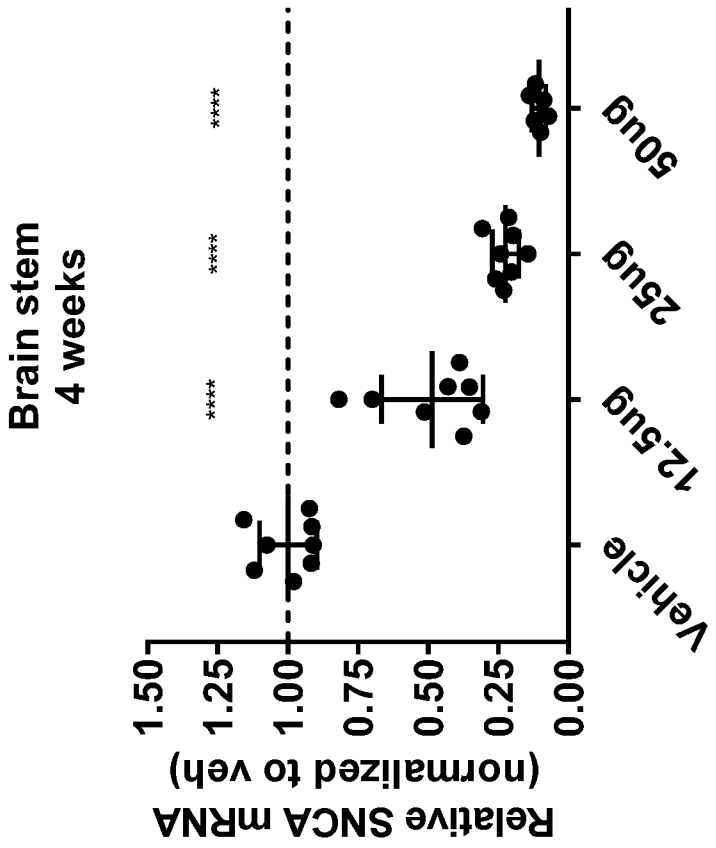


FIG. 10B

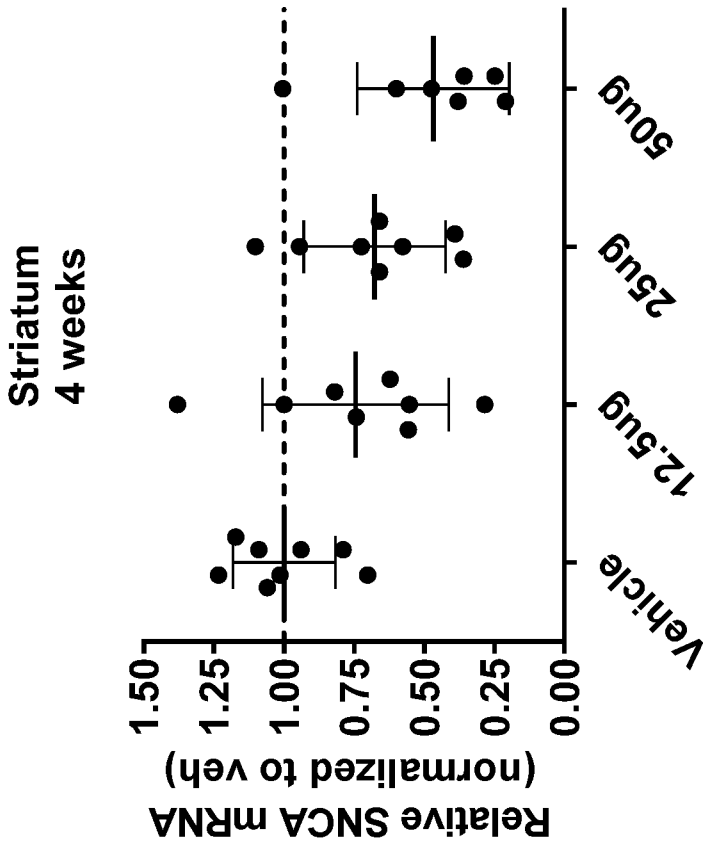


FIG. 11A

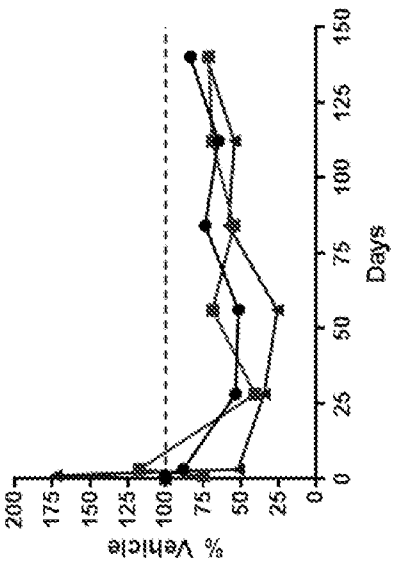


FIG. 11B

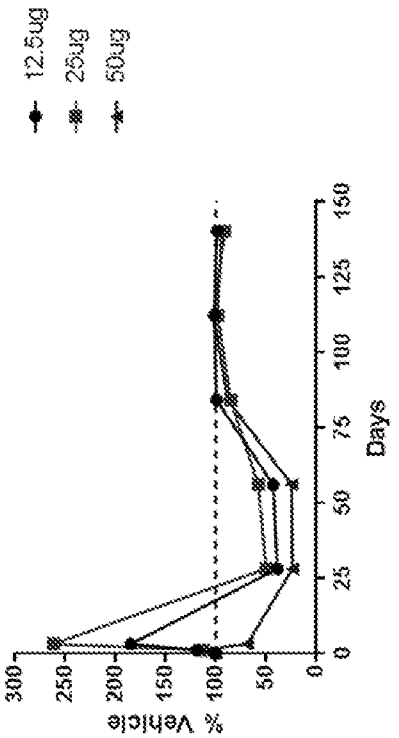


FIG. 12A

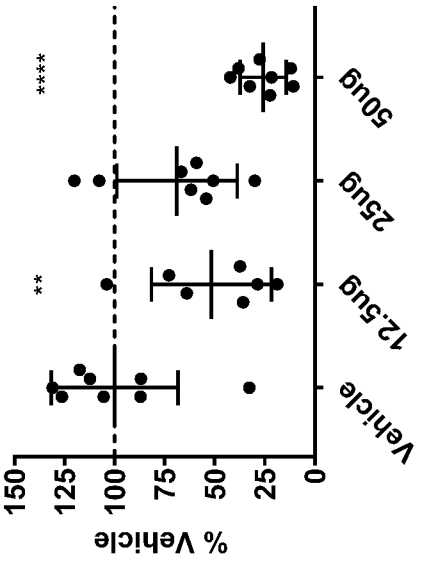


FIG. 12B

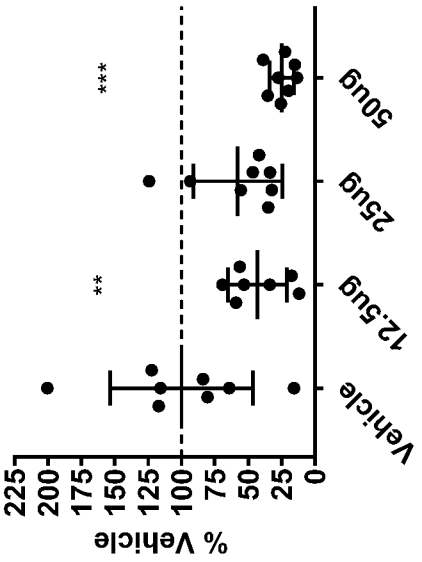


FIG. 13A

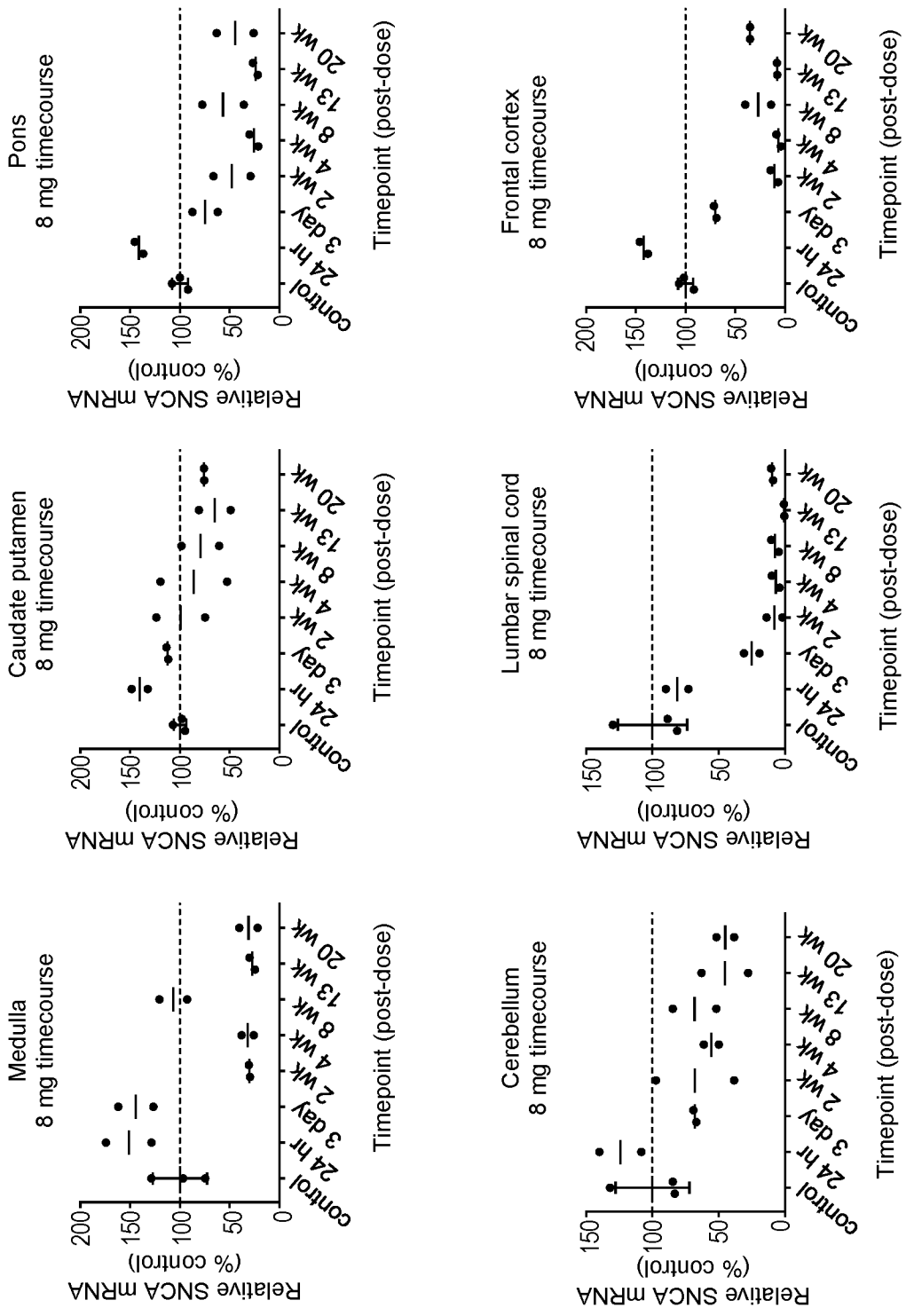
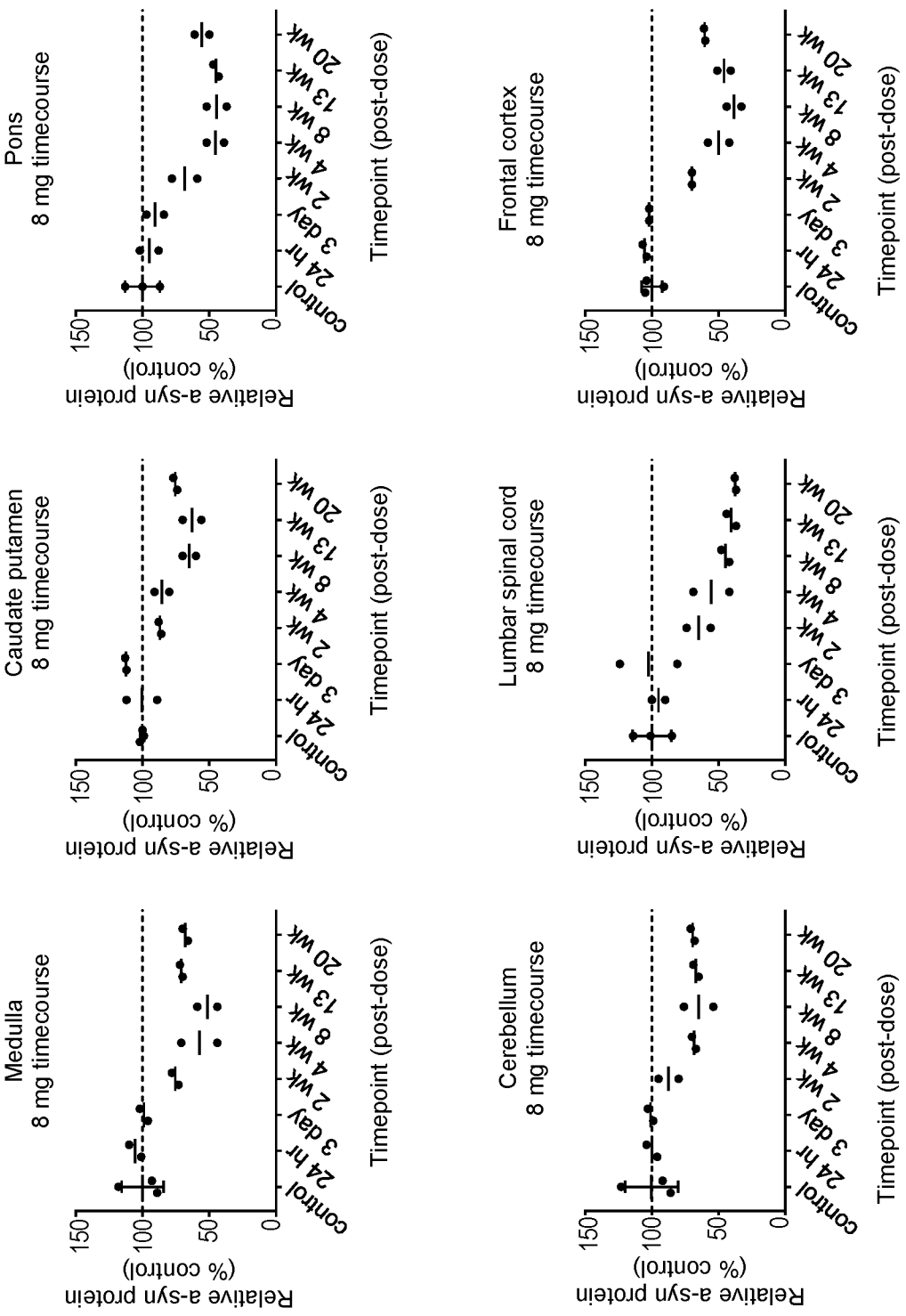

Pons
8 mg timecourse
Caudate putamen
8 mg timecourse
Frontal cortex
8 mg timecourse
Medulla
8 mg timecourse
Lumbar spinal cord
8 mg timecourse
Cerebellum
8 mg timecourse
Relative SNCA mRNA
(% control)
Timepoint (post-dose)
control
24 hr
3 day
2 wk
4 wk
8 wk
13 wk
20 wk
0
50
100
150
200

FIG. 13B


Pons
8 mg timecourse
Caudate putamen
8 mg timecourse
Frontal cortex
8 mg timecourse
Medulla
8 mg timecourse
Lumbar spinal cord
8 mg timecourse
Cerebellum
8 mg timecourse
Relative a-syn protein
(% control)
150
100
50
0
control
24 hr
3 day
2 wk
4 wk
8 wk
13 wk
20 wk
Timepoint (post-dose)

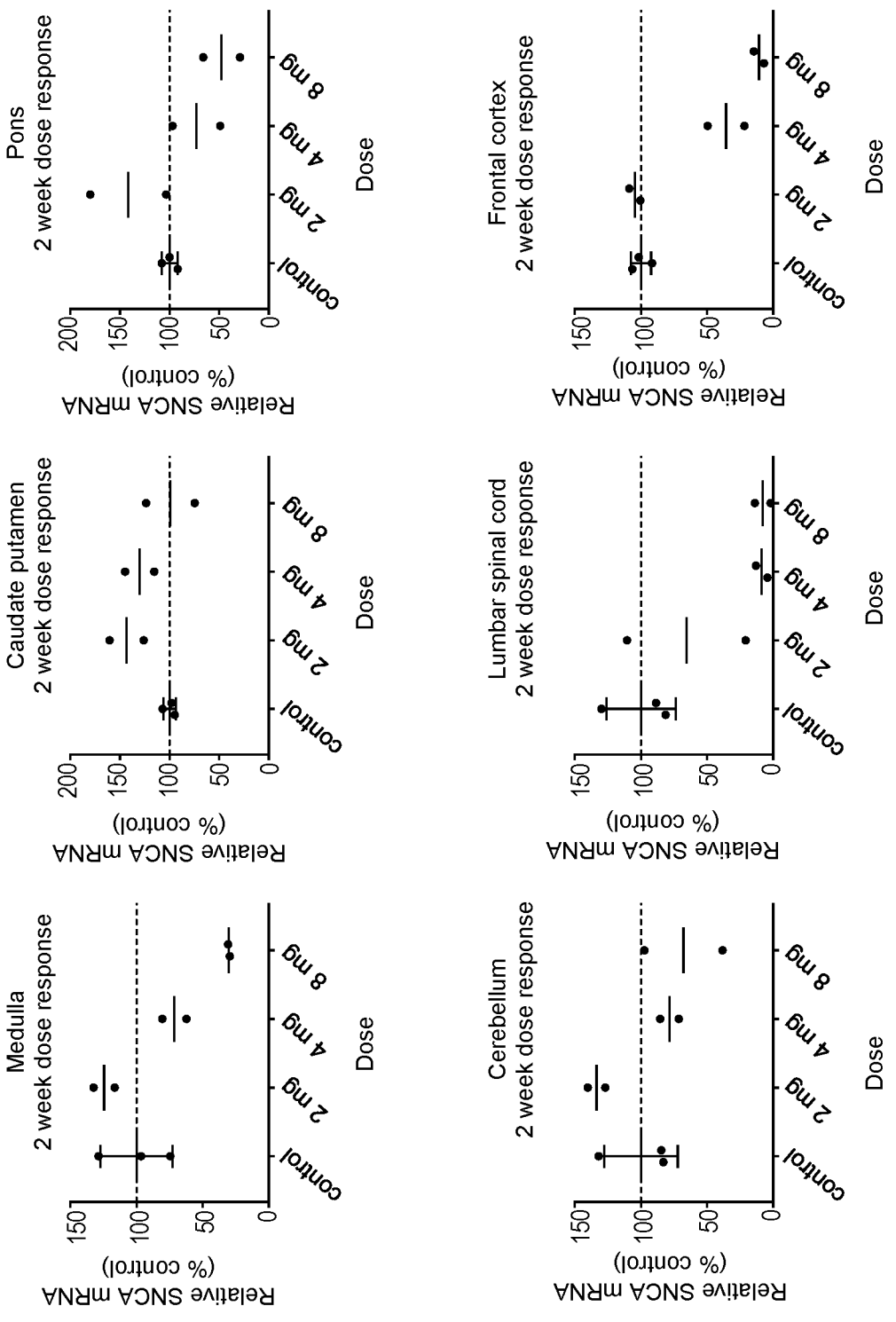

Pons
2 week dose response
Relative SNCA mRNA
(% control)
200
150
100
50
0
control
2 mg
4 mg
8 mg
Dose
Frontal cortex
2 week dose response
Relative SNCA mRNA
(% control)
150
100
50
0
control
2 mg
4 mg
8 mg
Dose
Caudate putamen
2 week dose response
Relative SNCA mRNA
(% control)
200
150
100
50
0
control
2 mg
4 mg
8 mg
Dose
Lumbar spinal cord
2 week dose response
Relative SNCA mRNA
(% control)
150
100
50
0
control
2 mg
4 mg
8 mg
Dose
Medulla
2 week dose response
Relative SNCA mRNA
(% control)
150
100
50
0
control
2 mg
4 mg
8 mg
Dose
Cerebellum
2 week dose response
Relative SNCA mRNA
(% control)
150
100
50
0
control
2 mg
4 mg
8 mg
Dose

FIG. 14A

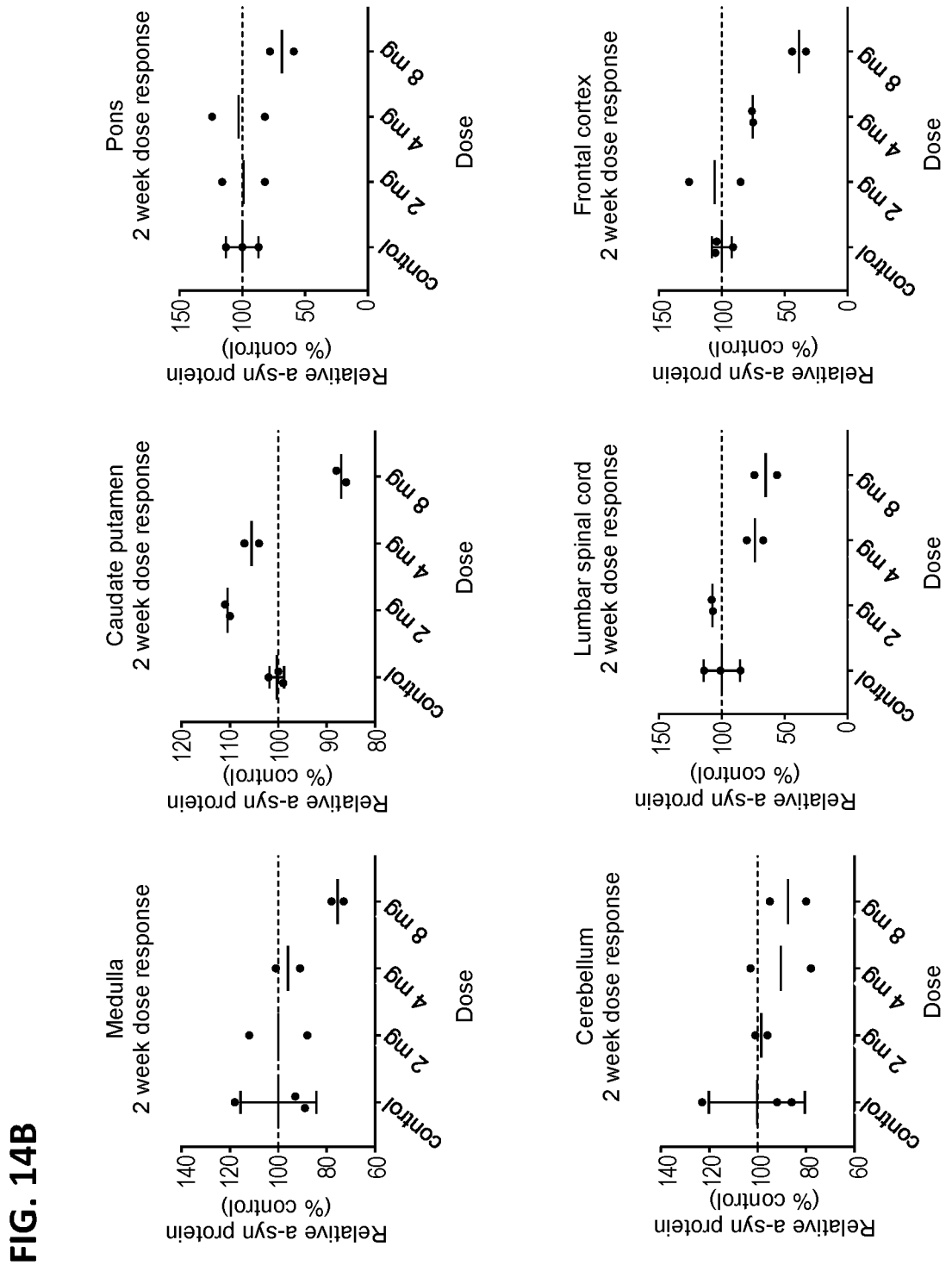

Medulla
2 week dose response
Relative a-syn protein
(% control)
140
120
100
80
60
control
2 mg
4 mg
8 mg
Dose
Caudate putamen
2 week dose response
Relative a-syn protein
(% control)
120
110
100
90
80
control
2 mg
4 mg
8 mg
Dose
Pons
2 week dose response
Relative a-syn protein
(% control)
150
100
50
0
control
2 mg
4 mg
8 mg
Dose
Cerebellum
2 week dose response
Relative a-syn protein
(% control)
140
120
100
80
60
control
2 mg
4 mg
8 mg
Dose
Lumbar spinal cord
2 week dose response
Relative a-syn protein
(% control)
150
100
50
0
control
2 mg
4 mg
8 mg
Dose
Frontal cortex
2 week dose response
Relative a-syn protein
(% control)
150
100
50
0
control
2 mg
4 mg
8 mg
Dose

FIG. 14B