# Unilateral Lesions of the Hippocampus Result in Circling Behavior; Effects on the Dopamine System

Tadzia J. GrandPre'

Washington and Lee University

Running head: UNILATERAL HIPPOCAMPAL LESIONS AND CIRCLING BEHAVIOR

# Unilateral Lesions of the Hippocampus Result in Circling Behavior; Effects on the Dopamine System

Tadzia J. GrandPre'

Washington and Lee University

Abstract

Rotational behavior, induced by unilateral lesions of a number of brain regions has long been studied as a model of various dopamine- (DA) related diseases. The hippocampal formation is interconnected with many of the brain's DA systems and is therefore potentially involved in modulation of DA-related diseases. The present study investigates unilateral hippocampal lesions, generated with either kainic acid (KA) and ibotenic acid (IBO), and subsequent rotational behavior. The results demonstrate that animals with unilateral KA hippocampal lesions exhibit significantly more rotation towards the side of the lesion immediately following surgery than either IBO lesioned animals or controls. Challenges with DA agonists at least 2 weeks post-surgery did not induce significant differences in rotational behavior. It appears that the former finding is a viable phenomenon which deserves further study.

## Unilateral Lesions of the Hippocampus Result in Circling Behavior; Effects on the Dopamine System

The incidence of rotational behavior, induced by unilateral lesions of a number of brain regions and subsequent drug challenges has been studied for a number of years. The most common model of rotation seems to involve animals with unilateral lesions of the mesencephalic DA neurons (e.g. Ungerstedt, 1971; Costall, Marsden, Naylor, & Pycock, 1976; Garrett & Holtman, 1996). This work has as its primary purpose the elucidation of the brain's motor system. It was recently observed in our laboratory that immediately upon waking from the anesthetic used during unilateral hippocampal lesioning, rats exhibited a marked preference for rotation in one particular direction. Since an involvement of the hippocampus in rotation had not been reported previously, this suggests that the hippocampal formation may have a modulating effect on the motor system.

From 1968 to 1971, Ungerstedt published a series of papers describing the degeneration of the nigro-striatal DA system in the rat brain and the rotational behavior and postsynaptic supersensitivity which result from such damage (e.g. Ungerstedt, 1971). Since that time, many studies have been published verifying Ungerstedt's findings, describing the results of variations of his original techniques, and hypothesizing about the mechanisms which produce the behavioral and physiological changes observed following damage to the nigro-striatal and mesolimbic DA systems.

Schwarting and Huston (1996a) discuss the behavioral and physiological changes resulting from damage to the mesencephalic DA system. Studies of this nature are primarily concerned with the

efferents of the ventral mesencephalon. There are three sub-groups of DAergic cell bodies in this region: the ventral tegmental area (VTA), the substantia nigra pars compacta (SNc), and the retrorubal area. The VTA projects to the nucleus accumbens (NAcc), the olfactory tubercle, the medial frontal cortex, the lateral septum, and the neostriatum, while the SNc projects primarily to the neostriatum and the retrorubral area projects to the tail of the neostriatum. These DAergic fibers travel in the nigro-striatal pathway and the medial forebrain bundle and the majority of these fibers innervate the ipsilateral hemisphere with no more than 5% projecting to the contralateral side. Lesions of these neurons, made with the toxin 6-hydroxydopamine (6-OHDA), result in DA depletions in the dorsal subdivision of the neocortex and the NAcc. These DA depletions manifest in a variety of behavioral and physiological changes, the most conspicuous of which is rotational behavior.

Studies have been published describing the incidence of spontaneous rotational behavior following unilateral 6-OHDA lesioning of mesencephalic DA neurons. In an early study, Ungerstedt (1971) reported observing spontaneous ipsilateral rotation (turning toward the side of the lesion) in rats during the first four weeks following the surgeries. Similarly, Matsuda, Akechi, Shimada, Terasawa, and Watanabe (1995) reported that rats with 6-OHDA lesions of mesencephalic neurons produced a total spontaneous rotation of over 100 turns per 12 hours in the night period (between post-operation days six and seven), 95% of which were in the ipsilateral direction. They further report that the percentage of ipsilateral rotation decreased slightly at the

second post-operative week but then remained at that level until sacrifice on the 31st post-operative day.

Considerably more common than the study of spontaneous rotational behavior following surgery is the examination of psychomotor stimulant drugs, usually amphetamine (AMPH) and apomorphine (APO), and their effects on the mesencephalic DA system. AMPH is considered an indirect DA agonist because it increases extracellular DA availability by elevating its release and decreasing its reuptake and degradation. Thus, due to the absence of DAergic neurons in the damaged hemisphere of 6-OHDA lesioned rats, administration of AMPH to those animals tends to enhance ipsilateral rotation. This increased turning behavior begins approximately ten minutes after systemic injection, reaches its peak within the first hour, and lasts from two to four hours. Further, extended studies have shown that injection of AMPH can produce ipsilateral rotation in 6-OHDA lesioned rats even two years post-lesion (Schwarting & Huston, 1996b). Garrett and Holtzman (1996) have demonstrated that the actual duration of both full and partial turning behavior, as well as the intensity of that behavior (i.e. the number of turns per minute) appear to be dose dependent. Very high doses of AMPH result in increases in directional change, presumably as the result of an overall boost in activity.

Unlike AMPH, APO is a DA receptor agonist which stimulates both the D1 and D2 families of receptors. Also unlike AMPH, administration of APO to 6-OHDA lesioned rats results in contralateral rotation (turning away from the side of the lesion). Schwarting and Huston (1996b) report that administration of APO

rapidly induces contralateral rotation in 6-OHDA lesioned rats after post-operative day one and up to at least day 200. Measurements made over a period of months, post-lesion, revealed increases in rotational behavior for up to at least three months with no further increase found after seven months. Like AMPH. APO appears to have dose-dependent effects on rotational behavior and high doses of APO result in an increased number of direction changes (Garrett & Holtzman, 1996).

These findings have led to extensive research on the mechanism by which DA agonist induced rotation occurs. Numerous studies have shown that in most systems, post-synaptic receptors are upregulated in order to compensate for the decrease in neurotransmitter release resulting from damage to the nerve terminals which control the receptors. This mechanism appears to hold for the D2 family of receptors following damage to the DA neurons of the mesencephalic DA system. There is still some controversy over the effects of 6-OHDA lesions on D1 receptors. Different investigators have claimed that the D1 receptors remain unchanged, are upregulated, and even that they are downregulated as a result of the lesion (Iwata, Shimizu, Nomoto, & Fukuda, 1996).

The hippocampus is interconnected with the circuitry of the mesencephalic DA system and its targets (see Figure 1). Projections from the hippocampal formation provide excitatory, glutamatergic efferents to the NAcc (Yang & Mogenson, 1985). Through an anterograde- and retrograde- horseradish peroxidase (HRP) study, Kelley and Domesick (1982) determined that the subiculum and, to a lesser degree, the CA1 field of hippocampus

provide this input to the NAcc. Further, they discovered that HPR injections into the rostral aspect of the NAcc resulted in labeling of the dorsal regions of the hippocampus while posterior injections resulted in labeling in more ventral regions. Amaral and Witter (1995) support these findings contending that projections from the temporal levels of CA1 innervate the NAcc. Fibers from the subiculum are found to be distributed throughout the NAcc with the projection to the caudome-dial part of the accumbens being the most dense. These subicular projections appear to be predominately ipsilateral but also show a weak contralateral component. The work of Lopes da Silva, Arnolds, and Neijt (1984) provides electrophysiological support for these anatomical findings. Focusing on the efferents from the subiculum, they conclude that stimulation of the NAcc by the subiculum (through slow conducting fibers) resulted in excitatory unit responses of the accumbens which were sometimes followed by decreases in the firing rate which could last for hundreds of milliseconds. From this finding they concluded that local circuits with recurring inhibition may exist in the NAcc. However, they also suggest that the possibility of repetitive excitation should also be considered because some of the units within NAcc tended to fire repetitively.

More detailed explanations of the projections from the hippocampus to the NAcc are provided by Yang and Mogenson (1984 & 1985). Also using electrophysiological techniques, they found that both silent and spontaneously active neurons in the medial NAcc are activated through stimulation of the ipsilateral ventral subiculum and that this period of excitation was often followed by a period of inhibition. They further discovered that stimulation

of the ventral subiculum resulted in prolonged inhibition in the dorso-medial and ventral border of the NAcc. However, within the diagonal band of Broca, neurons were excited by hippocampal stimulation. They also noted that stimulation of the VTA (train of 10 pulses) prior to stimulation of the ventral subiculum (single pulse) attenuated the excitatory responses of the neurons of the medial accumbens but did not affect the inhibitory responses of the neurons along the dorso-medial and ventral border of the accumbens. Others, such as Strecker and Monetal (1994) have proposed that increased DA may provide negative feedback to inhibit increased glutamatergic input.

From these investigations it is clear that the hippocampal formation, especially the subiculum, has a modulating effect on the NAcc and, subsequently, on the motor system of the rat. The present study was designed to investigate the effects of removal of hippocampus on the motor system. It was predicted that unilateral destruction of the hippocampus would result in rotational behavior comparable to that seen following damage to the nigro-striatal and mesolimbic DA systems. To test this hypothesis, unilateral KA and IBO lesions of hippocampus were used in rats. Rats were observed, videotaped, and scored for rotational behavior immediately following surgeries as well as following drug challenges with either AMPH or APO. This work is potentially important to the understanding of the neuroanatomical aspects of hippocampal projections to the motor system. In addition, it may increase knowledge of the role of DA in behavior as well as the brain's ability for recovery or compensation following hippocampal damage. Finally, this work may prove useful in the study and

treatment of schizophrenia and other DA related diseases.

## Method

### Animals

Male Sprague-Dawley rats (n=24) were individually housed in a temperature controlled colony room with a 12 hour light to 12 hour dark cycle. Animals were given free access to food and water.

### Unilateral hippocampal lesions

Under avertin anesthesia, rats were placed in a stereotaxic frame and the skin over the skull was retracted. Stereotaxic measurements were taken according to bregma and a bone flap was then removed over the area to be lesioned. In the experimental animals a total of 15 injection sites resulted in lesion of either the right or the left hippocampus (see Table 1). These lesions were made with KA (2 mg/ml, n=10) or IBO (10 mg/ml, n=7). A total of 1.03 µl of the toxin was injected into each animal. Individual injections were made in 20 sec. periods followed by an additional 20 sec. before removal of the micropipette to permit diffusion.

### Behavioral testing

Immediately following surgeries, animals were placed in individual cylindrical enclosures (12" diameter x 10" high) and videotaped for approximately six hours, after which they were returned to their home cages. At 14 and 21 days post-operation, the animals received a drug challenge of either APO (3 mg/kg, s.c., n=6) or AMPH (3 mg/kg, i.p., n=6), were placed back into the cylindrical enclosures, and were again videotaped (4 of the KA lesioned animals and 1 of the IBO lesioned animals did not undergo the drug procedure, they were used for a separate pilot

experiment). In addition to these experimental animals, 7 control animals (3 sham and 4 intact) underwent the same procedure. For all groups, drug administration was counterbalanced between animals (see Table 1). White noise was used during all videotaped sessions.

Scoring

Videotaped recordings of both experimental and control animals were scored for rotational behavior. Both wide and narrow rotation was recognized and animals were scored for the number of complete 360° turns made either ipsilateral or contralateral to the lesion in 15 minute time blocks. During both the AMPH and APO conditions, animals were scored for the first hour after injection. However, it should be noted that in the immediate post-operative condition,the animals showed marked individual differences in the time they required to awake from the anesthetic and begin moving around within the enclosures. In agreement with previous observations, our laboratory found that the rats lesioned with IBO were inactive for longer periods following the operation than the animals lesioned with KA. This observation has also been reported by Kohler and Schwarcz (1983) who noted that animals lesioned with IBO were inactive for up to eight hours following surgery. Because of these differences, it was necessary to determine a presentation of these data which would best represent the animals' rotational behavior following the surgeries. To do so, data from the most active hour of each rat, that is, the series of four consecutive 15 minute blocks in which the rat showed the greatest number of turns (ipsilateral + contralateral).

As a result, scores of immediate post-operative rotation represent the rotational behavior of the rats at the peak of their activity over at least a six hour period.

Histology

Approximately 4 weeks after surgery, animals were euthanized and perfused with physiological saline and 10% formalin. Brains were removed and placed in a 30% sucrose solution overnight. Coronal sections were cut at 40 μm on a cryostat, mounted on gelatin-subbed slides, and stained with cresyl violet stain. Sections were then examined both to verify lesion placement and to determine the extent of any extra-hippocampal damage.

## Results

Anatomical

Histological examination of cell-stained brain section revealed fairly consistent patterns of damage within each experimental group. All animals within the KA lesioned group suffered extensive loss of both CA3 pyramidal cells and the hilus of the dentate gyrus. The size of the hippocampus had noticeably decreased on the lesioned side. Further, most of these animals had a substantial loss of cells in subiculum and amygdala. All but one of the IBO lesioned animals had almost complete loss of the cells of hippocampus proper (CA1-CA3); there was occasional slight sparing of medial dentate gyrus cells. Further, several of these animals suffered some degree of subiculum damage, though generally not to the extent of the KA lesioned animals. One IBO lesioned animal had sparing of some of the medial aspects of the hippocampus proper, but still had substantial damage in this

region (>50%).

Mean total rotations

Figure 2 depicts the mean total rotations (over a one hour period) of each group (controls, KA lesioned animals, and IBO lesioned animals) in each of the three conditions (no drug: immediate post-operative, AMPH challenge, and APO challenge). Examination of this figure suggests that the KA and IBO lesioned animals appear to have made a greater number of total rotations than controls. This observation was confirmed by analysis of these data; a repeated-measures ANOVA revealed a significant group effect ($F(2,17) = 6.93$, $p = 0.006$). Subsequently, post hoc testing verified that the experimental animals made significantly more rotations than controls (Newman-Keuls, $p < 0.05$). Thus, unilateral removal of the hippocampus appears to increase locomotor activity. The condition x group interaction approached but did not attain significance ($F(4,34) = 2.1$, $p = 0.053$).

Immediate post-operative rotation

Figure 3 depicts the rotational behavior of animals in all three groups in the immediate post-operative condition. Examination of this figure suggests that KA lesioned animals made a greater number of ipsilateral rotations than either IBO lesioned animals or controls. A separate analysis of these data (ipsilateral and contralateral rotations considered separately, data collapsed over time) confirmed this observation; it revealed a significant group x direction interaction ($F(2,21) = 3.59$, $p = 0.045$). A Newman-Keuls post hoc test verified that KA lesioned animals exhibited significantly greater levels of ipsilateral rotation than either IBO lesioned animals or controls ($p < 0.05$) .

Drug-induced rotation

The rotational behavior of animals in all three groups in the AMPH challenge condition is shown in Figure 4 and the APO challenge condition is represented in Figure 5. A repeated-measures ANOVA incorporating both data sets (ipsilateral and contralateral rotation considered separately, data collapsed both over time and over counterbalanced drug challenges) revealed a significant group effect ($F(2,16) = 5.13$, $p = 0.019$). A Newman-Keuls post hoc test showed that both KA and IBO lesioned animals made a significantly greater number of total rotations than controls ($p < 0.05$). No significant interactions were found among any variables. Thus, animals with unilateral hippocampal lesions appear to be hypersensitive to DA agonists.

## Discussion

Immediate post-operative rotation

Hippocampal projections to the NAcc have been shown to play an important role in locomotor activity (e.g. Schacter, Yang, Innis, & Mogenson, 1989; Shen & Tsai, 1995; Brudzynski & Gibson, 1997). In the present study, animals with unilateral hippocampal lesions made with KA exhibited a significantly greater number of spontaneous ipsilateral rotations (immediately post-operative) than was observed in either IBO lesioned animals or control animals. The lack of a significant difference between the IBO lesioned animals and both the KA lesioned animals and the control animals is presumably attributable to their extended period of inactivity immediately following surgery and the immediate post-operative data from those animals should therefore be disregarded.

Diagram A of Figure 6 depicts a simplified view of rotational

behavior resulting from unilateral 6-OHDA lesioning of the mesencephalic DA neurons. Unilateral removal of DAergic efferents from the mesencephalic DA neurons to the ipsilateral NAcc results in ipsilateral rotation. Diagram B of Figure 6 illustrates a possible neuroanatomical and neurochemical model for the findings of the present study. Unilateral application of KA to the hippocampus results in ipsilateral rotation in the immediate post-operative condition. There appears to be a few possible explanations for this finding. First, many researchers have reported that efferents from the subiculum stimulate the NAcc and result in increased DA levels in the NAcc and subsequently in increased locomotor activity (e.g. Strecker & Moneta, 1994; Shen & Tsai, 1995; Brudzynski & Gibson, 1997). It follows that removal of those efferents, or at least the transmitter associated with those efferents (glutamate), should result in decreased activity in NAcc and therefore decreased locomotor activity. Because our design involves unilateral lesions, it is possible to observe overt behavioral changes (i.e. rotation) which may result from the unilateral reduction or depletion of glutamatergic efferents to the NAcc. However, this explanation is potentially problematic given the nature of the excitotoxin KA which destroys cells through overexcitation (Kohler & Schwarcz, 1983). The period of time necessary for destruction of cells through the use of KA is unknown. Thus, it is possible that during the time of our observation of ipsilateral rotation immediately following surgery, the NAcc was receiving excessive amounts of glutamate rather than reduced amounts.

It is therefore necessary to consider alternative

explanations for the findings of the present study. As can be seen in Figure 1, the hippocampus also has efferents to the prefrontal cortex. Some researchers have reported that an inverse relationship exists between DA levels in the prefrontal cortex and DA levels in the NAcc (e.g. Lipska, Jaskiw, Chrapusta, Karoum, & Weinberger, 1992). Further, DA levels in the prefrontal cortex appear to be modulated by hippocampal glutamatergic input such that neonatal lesions of hippocampus lead to reduced prefrontal DA metabolism in adulthood which in turn results in enhanced DA transmission between mesencephalic DA neurons and the NAcc (Kalivas & Sorg, 1996). Taking these findings into consideration, Diagram C of Figure 6 provides a second possible model for the neuroanatomical and neurochemical events leading to the findings of the present study. Unilateral overstimulation of hippocampal targets through the use of KA may result in excessive glutamate release in the ipsilateral hemisphere of the prefrontal cortex. This, in turn, may lead to a unilateral increase in glutamate transmission from the prefrontal cortex to the mesencephalic DA neurons followed by a reduction in mesencephalic DA release to the NAcc on the ipsilateral side. This mechanism should result in ipsilateral rotation. Once again, this explanation is problematic as it assumes that modulation of mesencephalic DA release by prefrontal cortex overrides modulation of NAcc excitation by the hippocampus.

A third possible explanation for the findings of the present study relate to the epileptogenic nature of KA. Injection of KA into the hippocampus leads to seizure activity and subsequently, to neuronal loss distant from the injection site (Kohler &

Schwarcz, 1983; Jarrard & Meldrum, 1993). Thus, it is possible that the overexcitation of hippocampal targets other than the NAcc or the prefrontal cortex may be directly or indirectly responsible for the ipsilateral rotation observed immediately following surgery.

Drug-induced rotation

Our laboratory found that animals with unilateral lesions of the hippocampus exhibit a greater increase in locomotor activity in response to administration of the DA agonists AMPH and APO than do controls. Similar findings have been described following administration of various DA agonists to animals with bilateral hippocampal lesions; these reports suggest that under such conditions, there is an increase in both pre- and post-synaptic DA transmission in the NAcc (Kalivas, 1995) and, conversely, a reduction of DA transmission in the prefrontal cortex (Sorg & Kalivas, 1993).

Our laboratory also found that no significant effect on direction of rotation was induced in the experimental groups when they were challenged with either AMPH or APO. This finding may be interpreted in at least three ways. First, it is possible that unilateral lesions of hippocampus have little or no differential impact on the DA system and that the difference in the number of immediate post-operative spontaneous ipsilateral rotations between groups and the group effect following DA-agonist administration are the result of a non-DA related mechanism. However, this possibility seems unlikely given the amount of literature which points to the modulating effect of hippocampus on NAcc. For example, the work of Lipska, Jaskiw, Chrapusta, Karoum, and

Weinberger (1992) shows that approximately 28 days after bilateral IBO lesions of the ventral hippocampal formation in rats there are increases DA levels in NAcc while simultaneously decreasing DA levels in the medial prefrontal cortex. Brudzynski and Gibson (1997) report that stimulation of the ventral subiculum of the hippocampal formation with NMDA significantly increased extracellular DA in the NAcc by 40% over baseline. It can be inferred from these studies, and many others, that unilateral lesions of hippocampus should affect the DA system.

A second, and perhaps more plausible explanation for the lack of significant effects of DA agonist challenges on direction of rotation in our animals is that our study has simply not yet incorporated enough animals. There are only six animals in each experimental group and the variability in our data is substantial. This explanation can, and will be rejected or supported through the addition of subjects into this study.

Finally, the best explanation for our results may be found in the lesions used in this study. The hippocampal lesions done with IBO may simply be ineffective because of the minimal amount of subiculum damage they induce. KA hippocampal lesions produce substantially more subiculum damage than the IBO lesions, however, there may be at least two possible problems with these lesions: 1) the subiculum damage may not be complete enough to significantly decrease the amount of glutamate which reaches the NAcc and/or the prefrontal cortex from the subiculum. 2) KA induces seizure activity in animals which results in extensive extra-hippocampal damage. Jarrard and Meldrum (1993) report that hippocampal lesions performed with KA result in extensive extra-hippocampal damage

including damage in the subiculum, parasubiculum, entorhinal cortex, amygdala, neocortex, and thalamus (conversely, they showed that hippocampal lesions performed with IBO had no noticeable effect on structures outside of the hippocampus). It is conceivable that this extra damage resulting from KA lesions may "interfere" with the functioning of the subiculo-accumbens pathway and/or the motor system as a whole in ways which cannot yet be accounted for. Future studies will include animals with selective subiculum lesions.

## Conclusion

In summary, animals with unilateral KA lesions of hippocampus exhibit significantly greater ipsilateral rotation than both IBO lesioned animals and controls. The explanation for this finding is uncertain and a great deal of work remains to be done in this area. The subiculo-accumbens pathway and the DA projection to the NAcc from the mesencephalic DA neurons have both been implicated in a variety of clinical disorders including schizophrenia, and epilepsy. The findings of the present study may lead to future work on the hippocampal formation as a modulator of the DA system.

## References

Amaral, D. G., & Witter, M. P. (1995). Hippocampal formation. In The Rat Nervous System, 2nd Edition (pp. 443-493). New York: Academic Press.

Brudzynski, S. M., & Gibson, C. J. (1997). Release of dopamine in the nucleus accumbens caused by stimulation of the subiculum in freely moving rats. Brain Research Bulletin, 42, 303-308.

Costall, B., Marsden, C. D., Naylor, R. J., & Pycock, C. J. (1976). The relationship between striatal and mesolimbic dopamine dysfunction and the nature of circling responses following 6-hydroxydopamine and electrolytic lesions of the ascending dopamine systems of rat brain. Brain Research, 118, 87-113.

Garrett, B. E., & Holtzman, S. G. (1996). Comparison of the effects of prototypical behavioral stimulants on locomotor activity and rotational behavior in rats. Pharmacology. Biochemistry, and Behavior, 54, 469-477.

Iwata, S., Shimizu, T., Nomoto, M., & Fukuda, T. (1996). Characteristic upregulation of dopamine D1-receptor in rat striatum after 6-hydroxydopamine treatment. Japanese Journal of Pharmacology, 71, 255-258.

Jarrard, L. E., & Meldrum, B. S. (1993). Selective excitotoxic pathology in the rat hippocampus. Neuropathology and Applied Neurobiology, 19, 381-389.

Kalivas, P. W. (1995). Neural basis of behavioral sensitization to cocaine. In R. P. Hammer Jr. (Ed.). The Neurobiology of Cocaine (pp. 81-98). Boca Raton: CRC Press.

Kalvias, P. W., & Sorg, B. A. (1996). Animal models of

psychosis reveal involvement of hippocampal-cortcostriatal-mesencephalic circuitry. In R. J. Beninger, T. Palomo, & T. Archer (Eds.), Dopamine Disease States (pp. 463-475). Madrid: Editorial CYM.

Kelley, A. E., & Domesick, V. B. (1982). The distribution of the projection from the hippocampal formation to the nucleus accumbens in the rat: An anterograde- and retrograde-horseradish peroxidase study. Neuroscience, 7, 2321-2335.

Kohler, C., & Schwarcz, R. (1983). Comparison of ibotenate and kainate neurotoxicity in rat brain: A histological study. Neuroscience, 8, 819-835.

Lipska, B. K., Jaskiw, G. E., Chrapusta, S., Karoum, F., & Weinberger, D. R. (1992). Ibotenic acid lesion of the ventral hippocampus differentially effects dopamine and its metabolites in the nucleus accumbens and prefrontal cortex in the rat. Brain Research, 585, 1-6.

Lopes da Silva, F. A., Arnolds, D. E. A. T., & Neijt, H. C. (1984). A functional link between limbic cortex and ventral striatum: Physiology of the subiculum accumbens pathway. Experimental Brain Research, 55, 205-214.

Matsuda, H., Akechi, Y., Shimada, Y., Terasawa, K., & Watanabe, H. (1995). Relationship of the ipsilateral rotation in night period and striatal dopamine content reduction in unilateral nigrostriatal 6-OHDA lesioned rats. Brain Research, 686, 111-114.

Schacter, G. B., Yang, C. B., Innis, N. K., & Mogenson, G. J. (1989). The role of hippocampal-nucleus accumbens pathway in radial-arm maze performance. Brain Research, 494, 339-349.

Schwarting, R. K. W., & Huston, J. P. (1996a). Unilateral 6-

hydroxydopamine lesions of meso-striatal dopamine neurons and their physiological sequelae. Progress in Neurobiology, 49, 215-266.

Schwarting, R. K. W., & Huston, J. P. (1996b). The unilateral 6-hydroxydopamine lesion model in behavioral brain research. Analysis of functional deficits, recovery, and treatment. Progress in Neurobiology, 50, 275-331.

Shen, A.-Y., & Tsai, C.-T. (1995). Neural connection from hippocampus to nucleus accumbens and the subpallidal area and their contribution to locomotor activity. Chinese Journal of Physiology, 38, 111-116.

Sorg, B. A., & Kalivas, P. W. (1993). Effects of cocaine and footshock stress on extracellular dopamine levels in the medial prefrontal cortex. Neuroscience, 53, 695-703.

Strecker, R. E., & Moneta, M. E. (1994). Electrical stimulation of the kindled hippocampus briefly increases extracellular dopamine in the nucleus accumbens. Neuroscience Letters, 176, 173-177.

Ungerstedt, U. (1971). Striatal dopamine release after amphetamine or nerve regeneration revealed by rotational behavior. Acta Physiologica Scandinavica, Supplement, 82, 49-68.

Yang, C. R., & Mogenson, G. J. (1994). Electrophysiological responses of neurons in the nucleus accumbens to hippocampal stimulation and the attenuation of the excitatory responses by the mesolimbic dopamine system. Brain Research, 324, 69-84.

Yang, C. R., & Mogenson, G. J. (1995). An electrophysiological study of the neural projections from the hippocampus to the ventral pallidum and the subpallidal areas by

way of the nucleus accumbens. Neuroscience, 15, 1015-1024.

# Hippocampal-Corticostriatal-Mesencephalic Circuitry

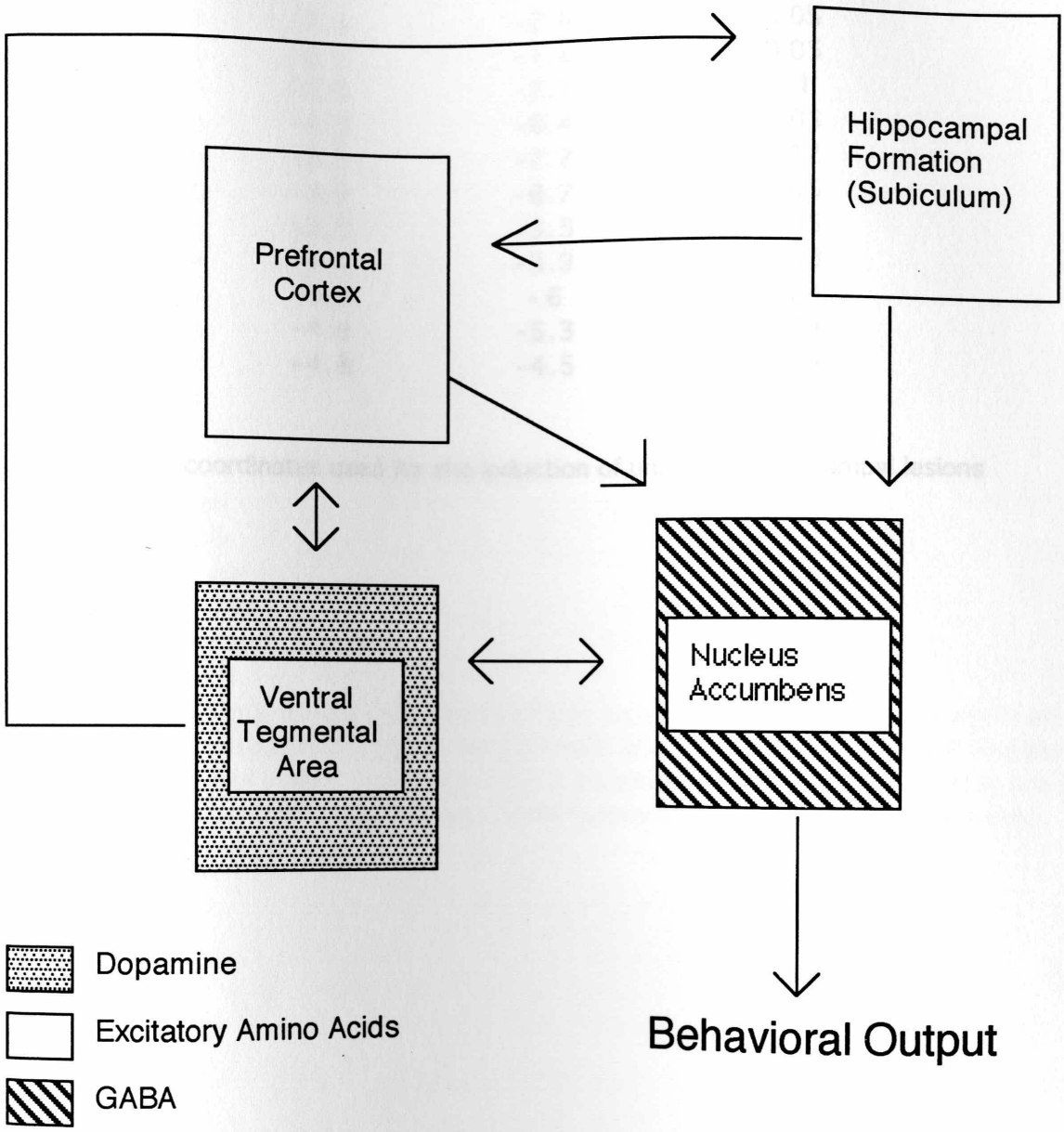


Figure 1

This figure is adapted from Kalivas & Sorg (1996)

| Stereotaxic coordinates Anterior/Posterior | Medial/Lateral | Dorsal/Ventral | Amount of toxin microliters |
|---|---|---|---|
| -2.4 | - 1 | - 3 | 0.05 |
| -3.1 | -1.4 | -2.9 | 0.05 |
| -3.1 | -1.4 | -2.1 | 0.05 |
| -3.1 | - 3 | -2.7 | 0.1 |
| - 4 | -2.5 | -2.8 | 0.05 |
| - 4 | -2.5 | -1.8 | 0.05 |
| - 4 | -3.6 | -2.7 | 0.1 |
| -4.9 | -4.5 | -6.4 | 0.05 |
| -4.9 | -3.9 | -7.2 | 0.12 |
| -4.9 | -3.9 | -6.7 | 0.05 |
| -4.9 | -3.9 | -3.5 | 0.05 |
| -5.7 | -4.1 | -3.9 | 0.08 |
| -5.7 | -4.8 | - 6 | 0.24 |
| -5.7 | -4.8 | -5.3 | 0.24 |
| -5.7 | -4.8 | -4.5 | 0.24 |

Table 1. Stereotaxic coordinates used for the induction of unilateral hippocampal lesions

## Experimental Design

| Rat number | Group | 14 days post-op | | 21 days post-op | |
|---|---|---|---|---|---|
| | | AMPH | APO | AMPH | APO |
| 1 | IBO | + | - | - | + |
| 2 | IBO | + | - | - | + |
| 7 | IBO | - | + | + | - |
| 8 | IBO | - | + | + | - |
| 9 | IBO | + | - | - | + |
| 10 | IBO | - | + | + | - |
| 4 | KA | + | - | - | + |
| 5 | KA | - | + | + | - |
| 6 | KA | - | + | + | - |
| 11 | KA | + | - | - | + |
| 12 | KA | - | + | + | - |
| 17 | KA | + | - | - | + |
| 13 | control | + | - | - | + |
| 14 | control | + | - | - | + |
| 15 | control | - | + | + | - |
| 16 | control | - | + | + | - |
| 18 | control (sham) | + | - | - | + |
| 19 | control (sham) | - | + | + | - |
| 20 | control (sham) | - | + | + | - |

Table 2. Drug challenges of animals of both experimental groups as well as control animals were counterbalanced to avoid confounds with drug interactions and timing of drug injection. In each lesion x order group there were 3 experimental animals and 2 unoperated controls. For sham controls, 2 animals were in one lesion x order group and 1 was in the other.

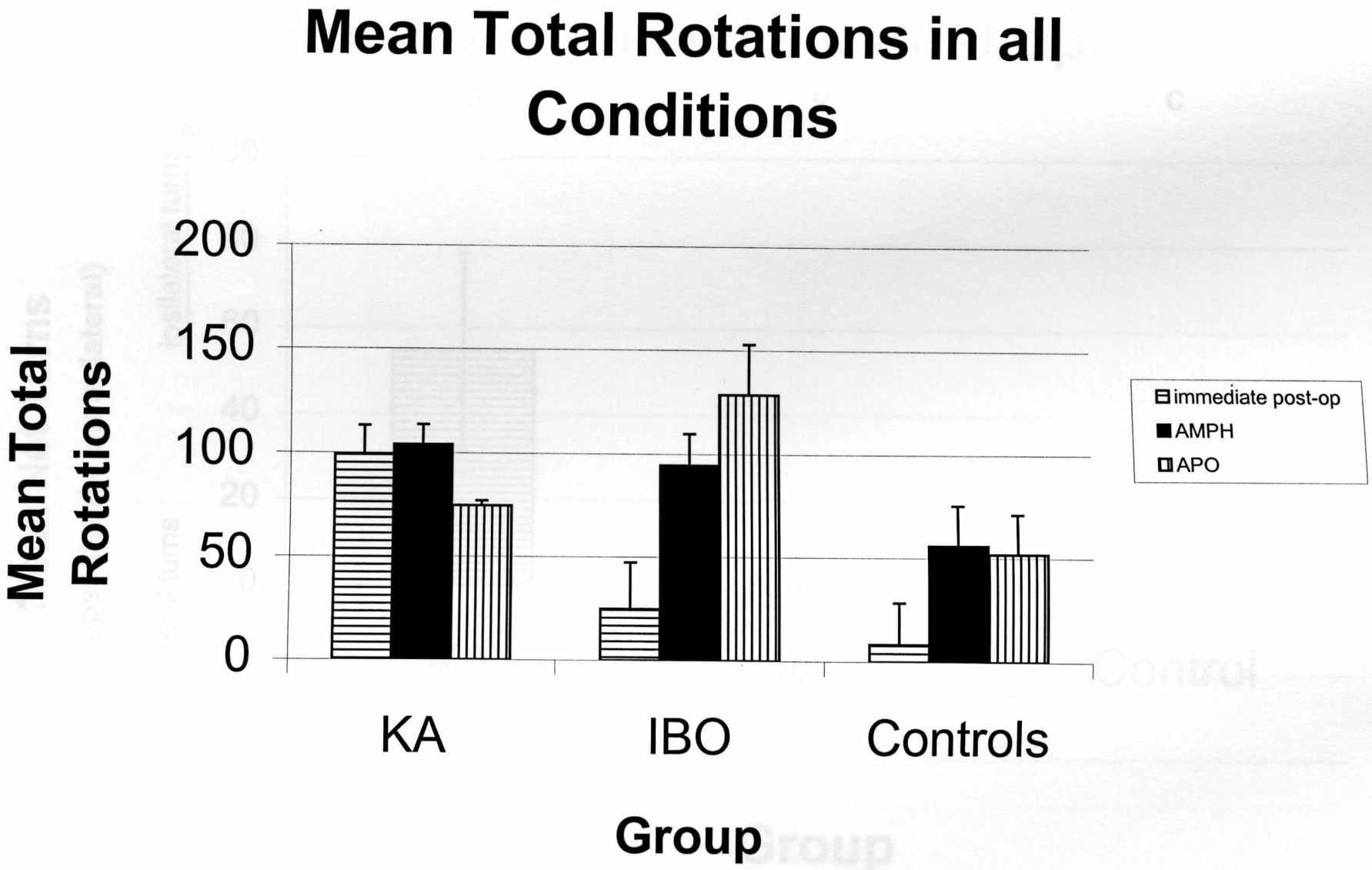


Figure 2. Mean total rotations made by each group under each condition over 60 min periods. Controls exhibited significantly fewer rotations than either group of experimental animals ($p < 0.05$).

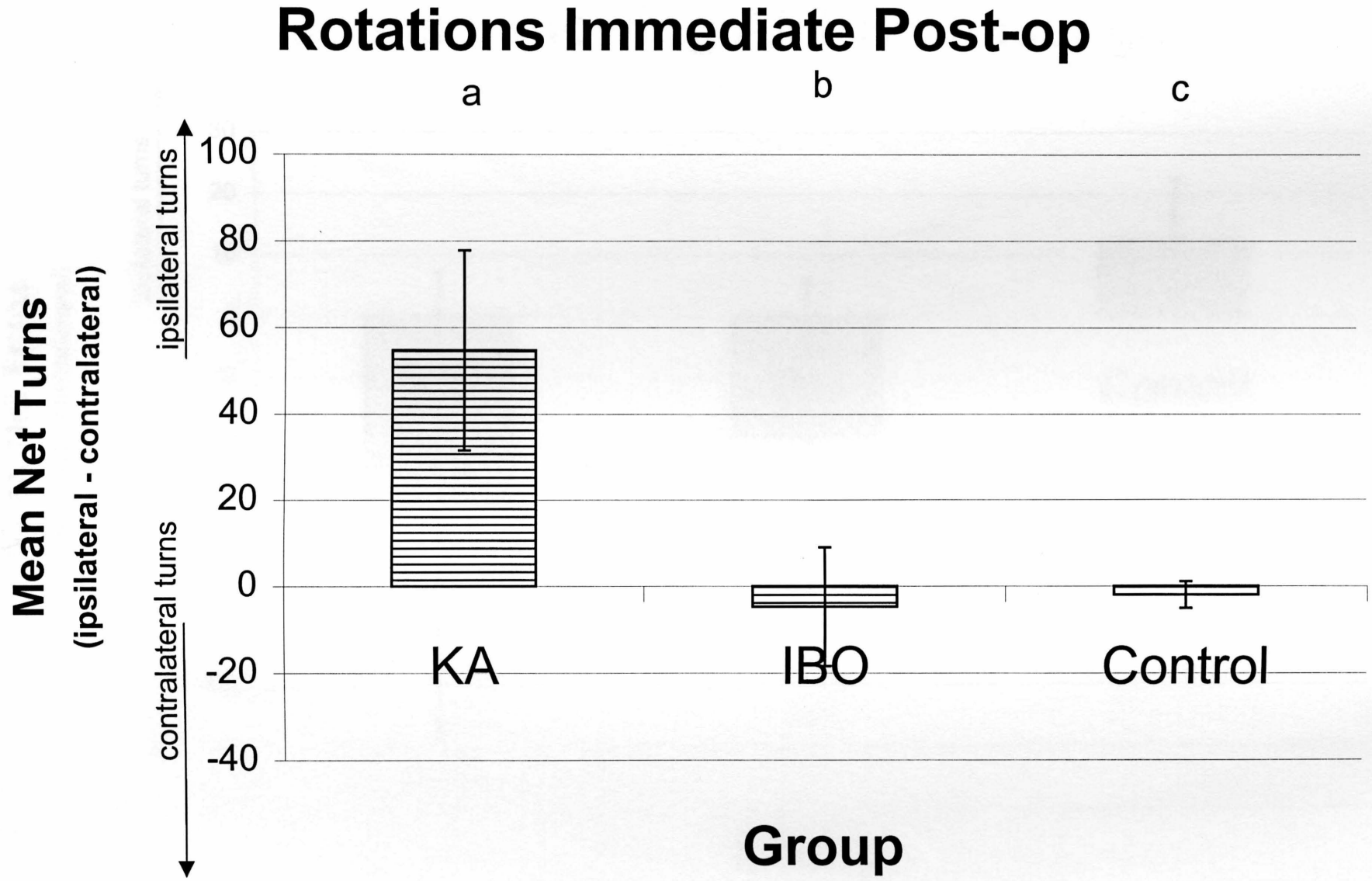


Figure 3. Mean net rotations made by animals immediately post-operative. A is significantly different from both B and C ($p<0.05$). Scores equal ipsilateral - contralateral turns (for controls, right - left turns).

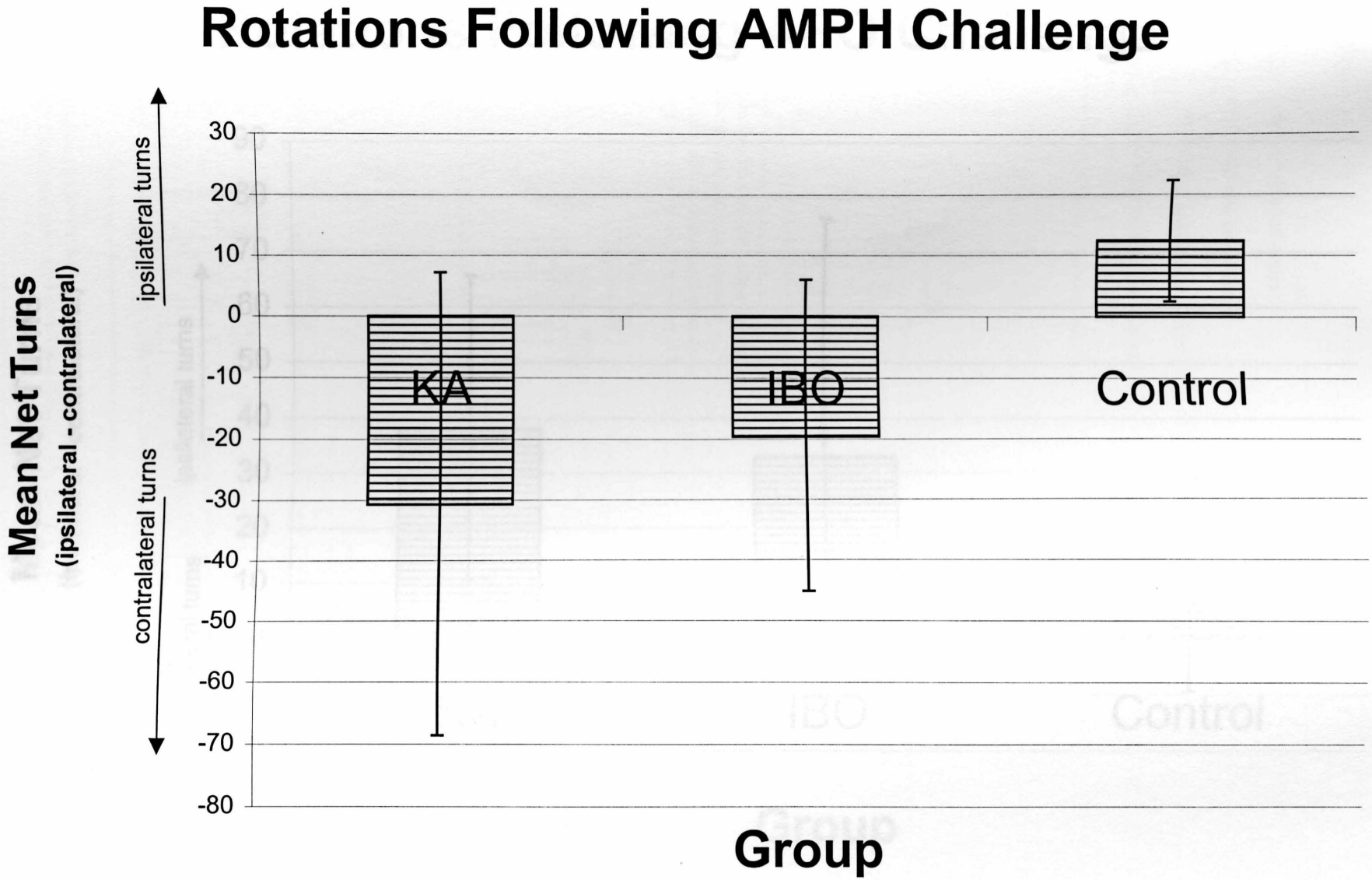


Figure 4. Mean net rotations (ipsilateral - contralateral) made by animals following challenge with AMPH (3 mg/kg) over a 60 min period.

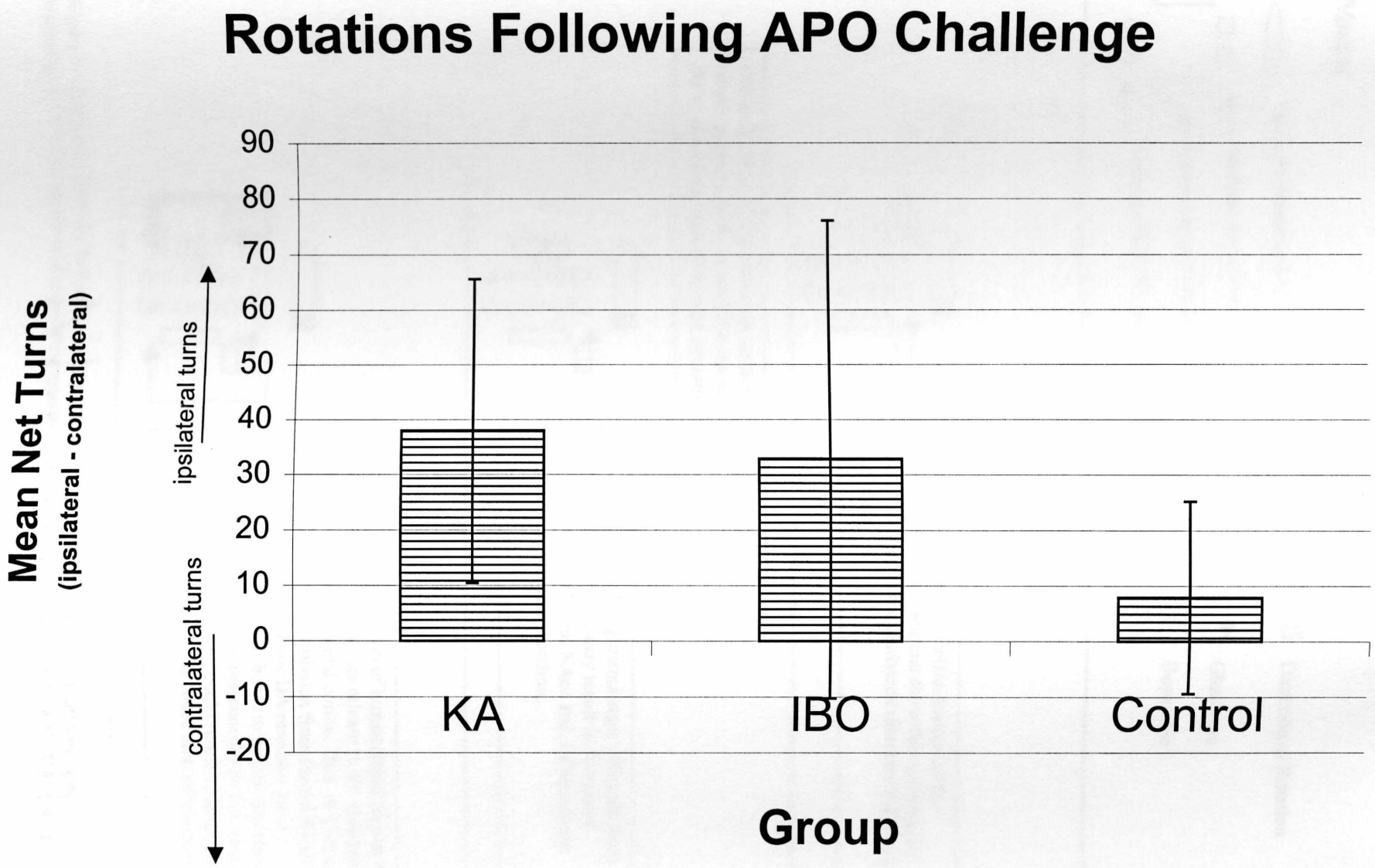


Figure 5. Mean net rotations (ipsilateral - contralateral) made by animals following challenge with APO (3 mg/kg) over a 60 min period.

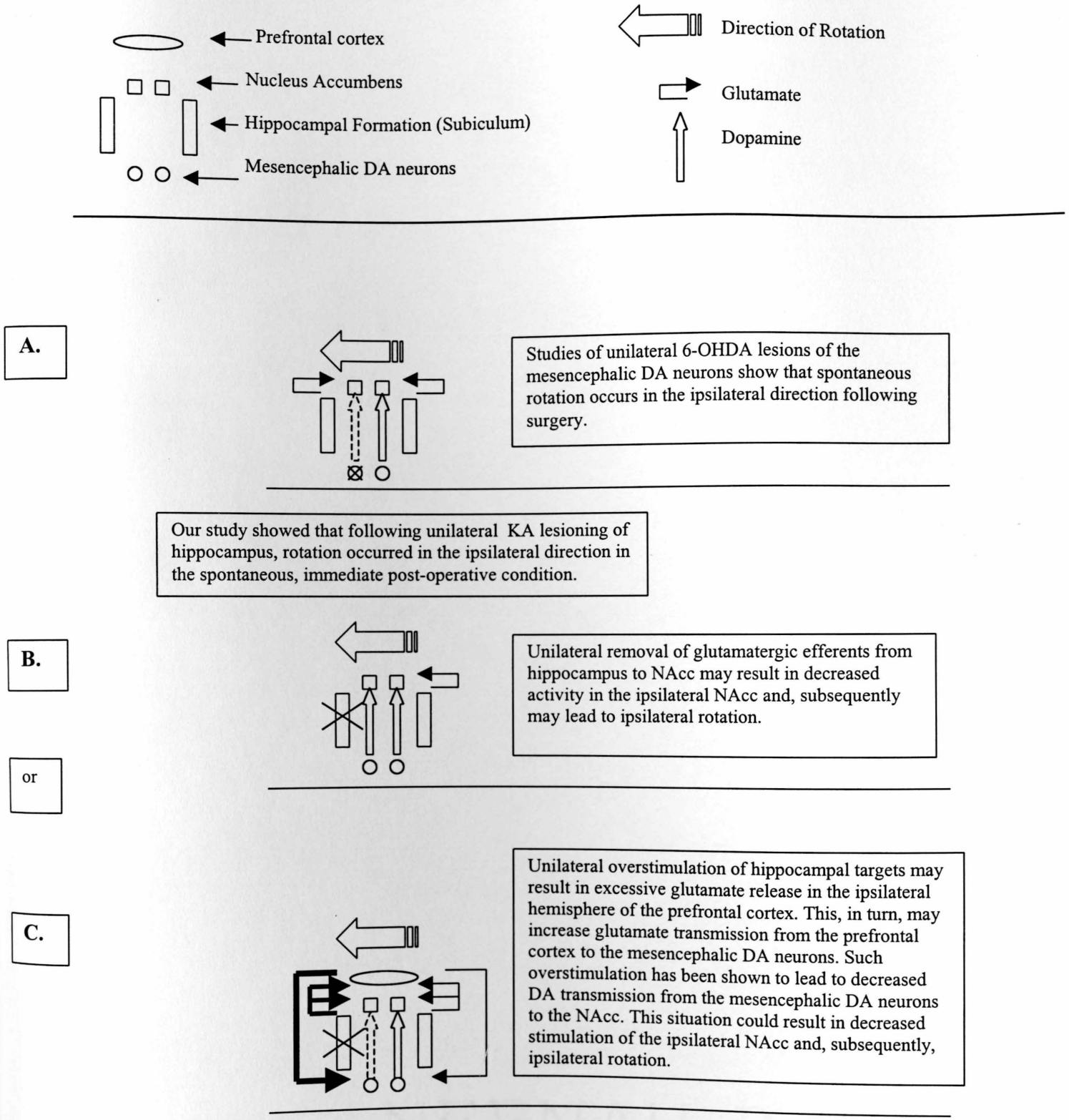


Figure 6. Rotational behavior following unilateral 6-OHDA lesioning and unilateral hippocampal lesioning. Thick lines represent increased transmission while dotted lines depict decreased transmission.