Pergamon

PII: S0306-4522(96)00377-6

*Neuroscience* Vol. 75, No. 1, pp. 5–12, 1996

Printed in Great Britain
0306–4522/96 $15.00+0.00

*Letter to Neuroscience*

# THE SUBSTANTIA NIGRA AS A SITE OF SYNAPTIC INTEGRATION OF FUNCTIONALLY DIVERSE INFORMATION ARISING FROM THE VENTRAL PALLIDUM AND THE GLOBUS PALLIDUS IN THE RAT

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*Key words*: basal ganglia, electron microscopy, GABA, dopaminergic neurons, convergence.

**Voluntary behaviour in mammals requires the integration of information from different parts of the cerebral cortex, notably the limbic, associative and sensorimotor areas, in a neural network that eventually controls the muscles.[25] One region of the brain that has been proposed to subserve such a function are the basal ganglia which receive inputs from all cortical areas. Although information from different cortical areas passes through the basal ganglia as a series of separate parallel pathways[2,15,19,21] there are several sites where integration of the diverse information could occur. In this study we identify a neural network at the synaptic level that may underlie a powerful mechanism for the integration, within the basal ganglia, of the diverse types of information arising from the cortex. By double anterograde tracing and immunocytochemistry at both the light and electron microscopic levels, we show that individual neurons in the substantia nigra pars reticulata and dopaminergic neurons in the pars compacta each receive multiple GABAergic synaptic inputs both from neurons in the ventral pallidum (which receive input from limbic areas via the nucleus accumbens[2,15,21]) and from neurons in the globus pallidus (which receive input from associative and sensorimotor cortices via the neostriatum[2,19,21]). Thus, information subserving functions such as emotion, motivation, cognition and movement converges onto basal ganglia output neurons, leading eventually to the muscles, and also on to the dopaminergic neurons which themselves subserve an integrative role by modulating the flow of information from the cortex through the basal ganglia at the level of the neostriatum and nucleus accumbens.**


One of the first clues that the basal ganglia might be a site of integration of functionally diverse information came from anatomical experiments which revealed that the major division of the basal ganglia, the neostriatum and its ventral homologue the nucleus accumbens, receive a topographical input from each of the functionally defined regions of the cortex.[2,9,14,15,19,21,23,24,25,28,35] It is also evident from functional analyses that the basal ganglia subserve an integrative role (e.g., see Refs 14a, 27, 37). The results of the anatomical analyses however, suggest that the segregation of functional information imparted by the topographical cortical input is maintained at each level of a series of segregated, parallel basal ganglia-thalamo-cortical loops.[2,15,19,21] The question arises therefore, where and how does the integration of functionally diverse information occur in the basal ganglia? Several systems have been proposed to subserve this function, including the local circuit neurons of the neostriatum and nucleus accumbens,[4,5,10,22] the ascending projections of midbrain dopamine neurons[12,20,25,29,33] and "open" cortico-basal ganglia-thalamo-cortical loops.[21] If integration does indeed occur within the basal ganglia, then it might also be mediated by distributed projections of the descending parallel pathways. There is, however, considerable debate as to whether or not these descending parallel pathways are completely functionally segregated.[1,26] Most of the data supporting the segregation of the descending systems have been derived from single neuronal tracing experiments in different

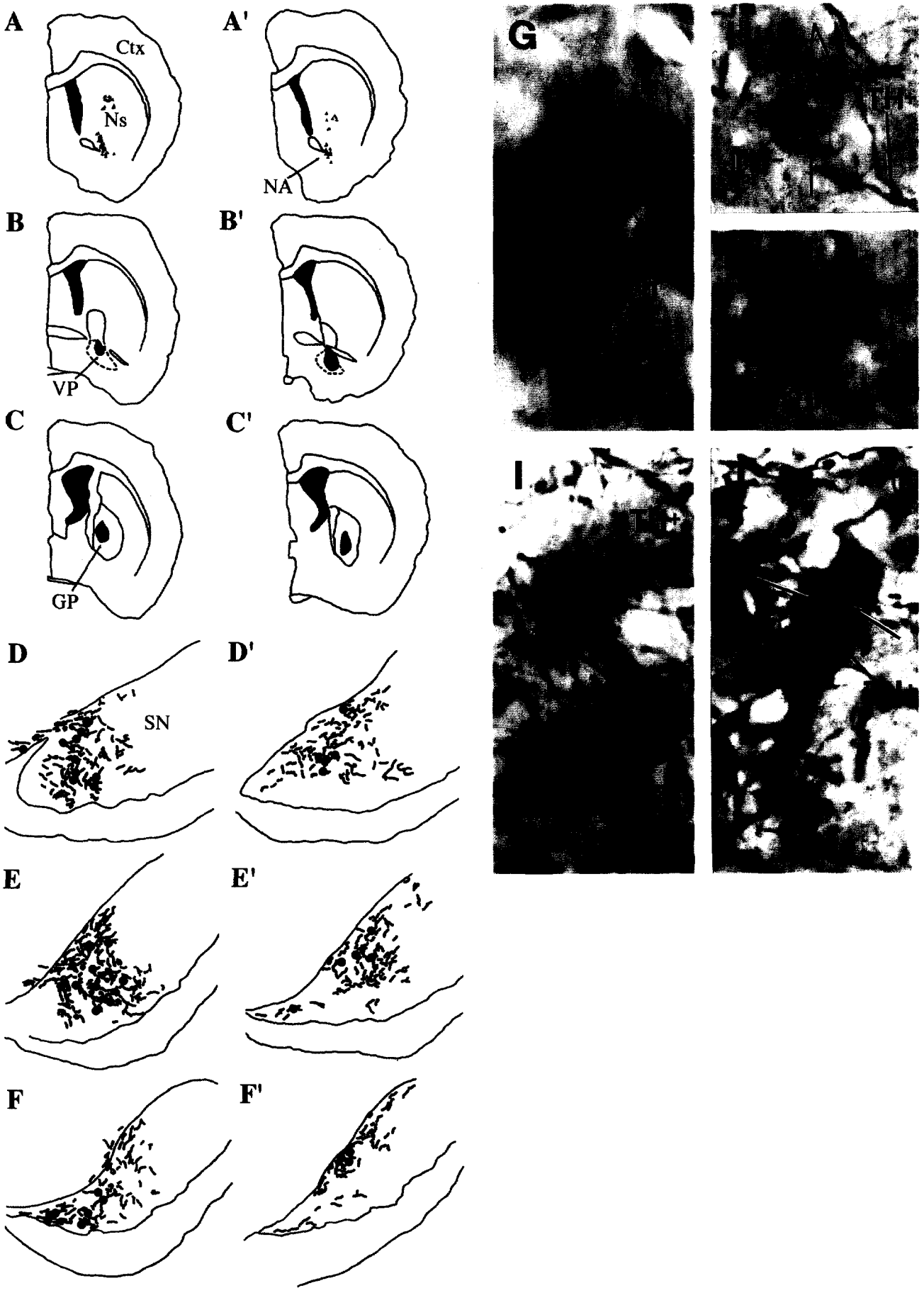
*Abbreviations*: ABC, avidin-biotin-peroxidase complex; BDA, biotinylated dextran amine; $b_{GP}$, terminals anterogradely labelled from the globus pallidus; $b_{VP}$, terminals anterogradely labelled from the ventral pallidum; GABA, gamma aminobutyric acid; GP, globus pallidus; NA, nucleus accumbens; NS, neostriatum; PAP, peroxidase-antiperoxidase complex; PHA-L, *Phaseolus vulgaris*-leucoagglutinin; SNC, substantia nigra pars compacta; SNR, substantia nigra pars reticulata; TH, tyrosine hydroxylase; VP, ventral pallidum.

experimental animals.[2,15,19,21] We have therefore addressed this question using double anterograde tracing in individual animals from two functionally distinct but homologous nuclei: the ventral pallidum, which mainly receives limbic information via the nucleus accumbens and the globus pallidus, which largely receives associative and sensorimotor information via the neostriatum.[2,11,13,15,17,19,21,38]

Five rats received injections of the anterograde tracers, *Phaseolus vulgaris*-leucoagglutinin (PHA-L) in the ventral pallidum and biotinylated dextran amine (BDA) in the globus pallidus. In an additional animal the injections were reversed; the pattern of labelling in this animal was similar to the others and will therefore not be described. In each animal the PHA-L injections were centred on the ventral pallidum (Fig. 1B, B′) and were predominantly confined to this structure, although an occasional PHA-L-labelled neuron was noted in the transitional zone between the globus pallidus and ventral pallidum. The BDA deposits were discrete and always completely confined to the globus pallidus (Fig. 1C, C′). The PHA-L and BDA injection sites did not overlap and were separated in the rostrocaudal plane by several hundred micrometres.

Light microscopic analysis of sections of the mesencephalon from these animals revealed, in confirmation of previous findings, that both the ventral pallidum[16] and the globus pallidus[30,31,32] densely innervate the substantia nigra and form basket-like clusters around individual neurons in both the pars compacta and pars reticulata. It was clear, however, that the labelled projections from the ventral pallidum and the globus pallidus to the substantia

Fig. 1. Individual dopaminergic and non-dopaminergic neurons in the substantia nigra are apposed by boutons anterogradely labelled from both the ventral pallidum and the globus pallidus. (A–F and A′–F′) Drawings of selected coronal sections from two representative rats that received injections of PHA-L in the ventral pallidum (B, B′; blue area denotes injection site; boundary of ventral pallidum indicated by dotted line) and BDA in the globus pallidus (C, C′; red area denotes injection site). Neurons retrogradely labelled with PHA-L (blue triangles) or BDA were observed in the nucleus accumbens or the neostriatum, respectively. The distribution of anterogradely labelled fibres (blue and red fibres represent PHA-L- and BDA-labelled fibres, respectively) and of neurons that were apposed by both PHA-L- and BDA-labelled varicosities on their proximal regions (black circles) in three representative sections of the substantia nigra from each animal are illustrated (D–F and D′–F′). The plots are of individual 60-μm sections and are not cumulative. (G–J) Individual neurons in the substantia nigra apposed by boutons labelled with PHA-L which was anterogradely transported from the ventral pallidum and revealed using nickel/3,3′-diaminobenzidine tetrahydrochloride (blue-black boutons, indicated by blue arrows) and boutons labelled with BDA which was anterogradely transported from the globus pallidus and visualized using 3,3′diaminobenzidine tetrahydrochloride (orange-brown boutons indicated by red arrows). (G) A neuronal perikaryon in the substantia nigra pars reticulata apposed by both sets of boutons. (H–H′) A neuron in the substantia nigra pars reticulata that is apposed by boutons from the ventral pallidum and the globus pallidus in a section that was also immunostained to reveal tyrosine hydroxylase using Vector VIP as the chromogen (immunoreactive elements are purple). Note that the neuron is not immunoreactive for tyrosine hydroxylase (TH-), whereas a dendrite displays the purple tyrosine hydroxylase reaction product (TH+). (I–J) Tyrosine hydroxylase-positive neurons (TH+) in the dorsal (I) and ventral (J) tiers of the substantia nigra pars compacta apposed by both sets of anterogradely labelled terminals. Scale bar in G=10 μm (applies to G–J). The double anterograde tracing combined with pre- and post-embedding immunocytochemistry at the light and electron microscopic levels was performed as described previously[32] except that biotinylated dextran amine was used as one of the tracers.[36] Under deep anaesthesia five rats received iontophoretic injections of PHA-L in the ventral pallidum and BDA in the globus pallidus and in another rat the tracer injections were reversed. Injections were made using previously reported parameters. Following a survival period of 1 week the animals were anaesthetized and then perfused with 0.1-0.5% glutaraldehyde and 2-3% paraformaldehyde. The brains were then sectioned at 60-μm intervals in the coronal plane. Two series of sections were processed for the light microscopic visualization of both tracers (antibodies and avidin-biotin-horseradish peroxidase complex (ABC; Vector) were diluted in phosphate buffered saline containing 0.3% Triton X-100). One of these series was also processed to reveal tyrosine hydroxylase immunoreactivity. Control experiments ensured no cross labelling of the tracers or neurochemicals. They were not detected when avidin-biotin-horseradish peroxidase complex and immunoreagents were replaced by normal serum. Colour mixing, an indicator that the chromogens were reacting with more than one of the three peroxidase layers was not observed. Biotinylated dextran amine was detected first (1:100 ABC) using 3,3′-diaminobenzidine tetrahydrochloride as chromogen, PHA-L was visualized second (1:500 rabbit anti-PHA-L; 1:100 goat anti-rabbit; 1:100 rabbit peroxidase-anti-peroxidase (PAP), DAKO) using 3,3′-diaminobenzidine tetrahydrochloride in the presence of nickel ions as the chromogen. Tyrosine hydroxylase was visualized last (1:1000 rabbit anti-tyrosine hydroxylase (see ref. 31); 1:100 biotinylated goat anti-rabbit, Vector; 1:100 ABC) using Vector VIP as the chromogen. Two other series of sections through the injection sites were processed to reveal substance P (1:50 rat anti-substance P;[7] 1:100 goat anti-rat, DAKO; 1:100 rat PAP, Incstar) or enkephalin (1:1,000 mouse anti-enkephalin, Sera-Lab; 1:100 goat anti-mouse, DAKO; 1:100 mouse PAP, DAKO) immunoreactivity using 3,3′-diaminobenzidine tetrahydrochloride. Substance P and enkephalin are markers of the ventral pallidum and globus pallidus and were used to determine the precise location of the injection sites.[15] All the sections were then mounted for light microscopic analysis and photography. In the light microscope BDA-labelled elements were brown, PHA-L-labelled elements were blue-black and tyrosine hydroxylase-immunopositive elements were purple.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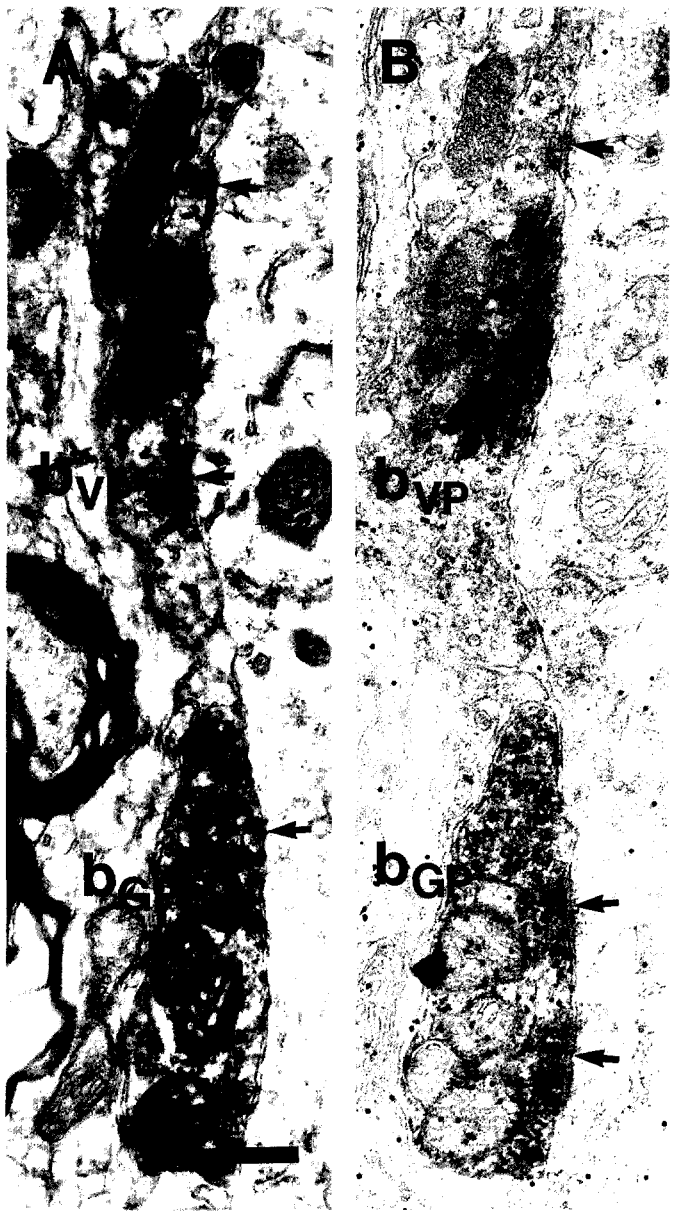



Fig. 2. Individual neurons in the substantia nigra pars reticulata receive convergent, GABA-immunopositive synaptic input from the ventral pallidum and the globus pallidus. (A,B) Electron micrographs of the soma of a neuron in the middle third (mediolateral and rostrocaudal axes) of the substantia nigra pars reticulata that displayed the morphological characteristics of a basal ganglia output neuron, i.e. low cytoplasm to nuclear volume ratio and a paucity of Nissl bodies.[8] The neuron receives symmetrical synaptic inputs (arrows) from terminals derived from the ventral pallidum (bVP; labelled with PHA-L and revealed using benzidine dihydrochloride) and the globus pallidus (bGP; labelled with BDA and revealed using diaminobenzidine). The diaminobenzidine reaction product which is amorphous and adheres to subcellular organelles can be distinguished from the benzidine dihydrochloride reaction product which forms dense crystalline aggregates. One of the sections was incubated to reveal GABA immunoreactivity using the post-embedding immunogold technique.[18,34] The high density of gold particles overlying the anterogradely-labelled terminals compared to known GABA-immunonegative terminals in the same section indicates that they are GABA-immunopositive (index of immunoreactivity of BDA-labelled terminal=4.45; PHA-L labelled terminal=3.9). Scale bar in A=0.5 $\mu$m (also applies to B). The majority of the brain sections were processed for correlated light and electron microscopic analysis.[31,32] All antibody incubations and peroxidase reactions were carried out as described above, except that Triton was not added and benzidine dihydrochloride was used as the chromogen to visualize PHA-L-labelled structures. The diaminobenzidine reaction product and the benzidine dihydrochloride reaction product were easily distinguished in the electron microscope on the basis of the texture and density of the peroxidase reaction products they contained. GABA immunoreactivity was detected on some ultrathin sections using the post-embedding immunogold method.[18,34] The GABA-immunoreactivity (density of immunogold particles overlying the bouton minus density of immunogold particles overlying tissue-free resin on that section) of the anterogradely labelled boutons was normalized for section to section, grid to grid and animal to animal variation in labelling efficiency by comparing it to that found in the population of GABA-immunonegative terminals forming asymmetrical synaptic contacts in the same ultrathin section. The ratio so obtained is called the index of immunoreactivity.

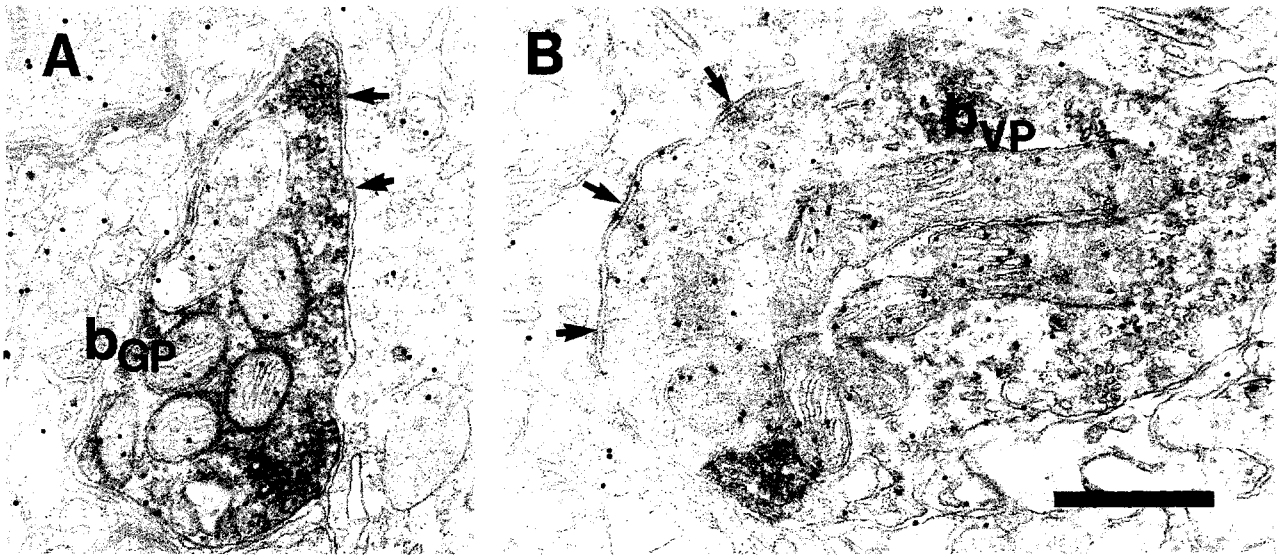
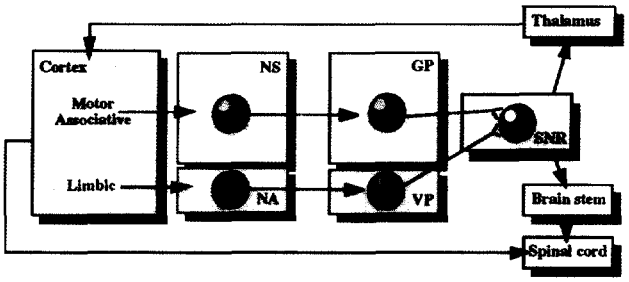



Fig. 3. Individual neurons in the substantia nigra pars compacta receive convergent, GABA-immunopositive synaptic input from the ventral pallidum and the globus pallidus. Electron micrographs of terminals anterogradely labelled from the globus pallidus (bGP) and the ventral pallidum (bVP) both of which make synaptic contact with the perikaryon of the same neuron in the medial substantia nigra pars compacta that displays the ultrastructural characteristics of a dopaminergic neuron, i.e. high cytoplasmic to nuclear volume ratio and many Nissl bodies.[8] The bouton bGP (A) was anterogradely labelled with BDA (diaminobenzidine reaction product) and the bouton bVP (B) was labelled with PHA-L (benzidine dihydrochloride reaction product located at the bottom left of the terminal) and both make symmetrical synaptic contacts (arrows). The ultrathin sections were also labelled for GABA using the post-embedding immunogold method.[18,34] A relatively high density of gold particles overlies the two anterogradely-labelled terminals indicating that they are GABA-immunopositive (index of immunoreactivity of bGP=4.78 and bVP=10.9). Scale bar in B=0.5 $\mu$m (also applies to A).

**Convergence in the substantia nigra *pars reticulata***




**Convergence in the substantia nigra *pars compacta***

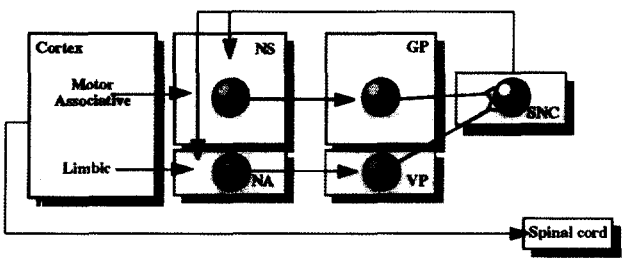



Fig. 4. Schematic diagram summarizing the neural network that underlies the role of the substantia nigra as a site of integration of functionally diverse information in the basal ganglia. Pathways are denoted by arrows. The term "Brain stem" denotes subcortical premotor areas innervated by the substantia nigra including the superior colliculus, the parvicellular reticular formation and the mesopontine tegmentum. NS, neostriatum; NA, nucleus accumbens; GP, globus pallidus; VP, ventral pallidum; SNR, substantia nigra pars reticulata; SNC, substantia nigra pars compacta.

nigra did not obey the simple topographical rule of segregation predicted by segregated, parallel processing models of basal ganglia function[2,15,19] but were in fact distributed and formed a complex interdigitating and overlapping network (Fig. 1D-F, D′-F′). In these regions of overlap individual neuronal perikarya and proximal dendrites of neurons in the substantia nigra were closely apposed by anterogradely labelled boutons derived both from the ventral pallidum and from the globus pallidus (Fig. 1D-F, D′-F′, G-J). In an individual section of the substantia nigra up to a quarter of the neurons apposed by boutons from the ventral pallidum or the globus pallidus were apposed by boutons from both sources. By combining immunocytochemistry for tyrosine hydroxylase (a marker for dopaminergic neurons in this region) and the visualization of the two anterograde tracers, we observed that both tyrosine hydroxylase-immunonegative neurons (putative output neurons) in the substantia nigra pars reticulata (Fig. 1H-H′) and tyrosine hydroxylase-immunopositive neurons (dopaminergic) in the substantia nigra pars compacta (Fig. 1I, J) were the targets of the convergent projections. Furthermore, dopaminergic neurons located in both the dorsal and ventral tiers of the pars compacta were apposed by both types of bouton (Fig. 1I, J).

Electron microscopic analysis of 11 neurons (four animals) that were first identified in the light microscope revealed that terminals anterogradely labelled from neurons in the ventral pallidum or in the globus pallidus did indeed make convergent synaptic contact with the perikarya and proximal dendrites of individual neurons in the substantia nigra (seven neurons in the pars reticulata and three neurons in the pars compacta; Figs 2, 3). Each axonal branch gave rise to multiple terminals which formed symmetrical synaptic contacts with the postsynaptic neuron. Furthermore each terminal was characterized by multiple sites of transmitter release (Figs 2, 3). Postembedding immunocytochemistry for GABA revealed that all the boutons anterogradely labelled from the ventral pallidum ($n$=6) and the globus pallidus ($n$=10) that were analysed were immunopositive for GABA (Figs 2B, 3).

Some retrograde labelling of neurons in the nucleus accumbens and the neostriatum occurred following the injections in the ventral pallidum and the globus pallidus, respectively (Fig. 1A, A′). It is unlikely that anterograde labelling from these striatal neurons to the substantia nigra confounded the present results because the anterogradely labelled terminals did not display the well-characterized ultrastructural features of terminals derived from the nucleus accumbens or the neostriatum.[32,33] The pattern of retrograde labelling did however, confirm that the injections of tracers in the ventral pallidum and the globus pallidus were into regions that were innervated by spatially and thus functionally different parts of the nucleus accumbens and the neostriatum[11,13,17,38] which in turn are innervated by different regions of the cortex.[2,15,19,21]

Although our data demonstrate that individual neurons in the substantia nigra receive convergent input from different functional regions of the pallidal complex it is unlikely that every neuron in the substantia nigra receives input from all functional territories of the pallidal complex. In view of the recognized topography of the descending projections it is more likely that individual neurons, in the pars reticulata at least, receive convergent input from neurons of neighbouring functional pathways.[16,30,31,32] Preliminary analysis suggests that this organizational principle also holds true for the subthalamic nucleus and the other output nucleus of the basal ganglia, the entopeduncular nucleus.[3]

The multiple innervation of neurons in the substantia nigra by individual pallidal neurons, the strategic location of their terminals on the cell body and proximal dendrites of their postsynaptic targets and their GABAergic nature, suggests that pallidal neurons exert powerful inhibitory control both over the output neurons of the basal ganglia and over the dopaminergic neurons.[16,30,31,32] The present findings suggest that this potentially powerful synaptic output of pallidal neurons may also underlie mechanisms by which different functional information is integrated in the basal ganglia. Neurons of the pallidal complex may thus play a critical integrative role in the basal ganglia by at least two mechanisms. First, they provide functionally diverse information directly to the output neurons of the basal ganglia thereby influencing the patterned basal ganglia output which results in inhibition and disinhibition of neurons in the thalamus and brainstem.[6] Secondly, they provide functionally diverse information to the dopaminergic neurons of the nigral complex that in turn provide a feedback that modulates the flow of information through the basal ganglia[12,20,25,29,33] (Fig. 4). In summary, the present results demonstrate that neurons of the pallidal complex are not only in a position to control the activity of dopaminergic and basal ganglia output neurons in the substantia nigra,[16,30,31,32] but are also capable of mediating interaction between information flowing through pathways subserving different functions such as emotion, motivation, cognition and movement.

*Acknowledgements*—The authors thank Liz Norman, Paul Jays, Caroline Francis and Frank Kennedy for technical assistance and Peter Somogyi and Claudio Cuello for the GABA and substance P antibodies, respectively. We also thank Peter Somogyi and Nick Clarke for comments on the manuscript. This work was funded by the Wellcome Trust and the Medical Research Council, U.K.

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(*Accepted* 15 *April* 1996)