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Action sequencing is impaired in D_{1A}-deficient mutant mice

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Abstract

The role of dopamine in the production of behaviour is multifarious in that it can influence different aspects of movement (e.g. movement initiation, sensorimotor integration, and movement sequencing). A characteristic of the dopamine system which seems to be critical for the expression of this diverse influence is its varied receptor population. Previous studies have shown that specific receptor subtype activation leads to specific behavioural responses or alterations of selective aspects of movement. It is known that one of the important influences of dopamine includes sequential co-ordination of 'syntactic' patterns of grooming movements because moderate loss of the dopaminergic nigrostriatal projections specifically disrupts these patterns without affecting grooming actions in a general fashion (Berridge, K.C. *Psychobiology*, **15**, 336, 1989). The specific receptors of the dopamine family which play a key part in this co-ordination of movement sequences is not known. In the present study, we examined the serial order of particular syntactic sequences or chains of grooming actions in mice lacking D_{1A} receptors to explore the relationship between this receptor subtype and movement sequencing. Mutant mice had shorter grooming bouts and a disruption of the organization of sequential patterns compared with wild-type littermate controls. Sequential disruption was reflected in the failure of D_{1A} mutants to follow the syntactic pattern of grooming to completion. This sequential disruption deficit appeared to be specific, as mutant mice initiated more syntactic chains than wild-type controls even though they were less likely to complete them. These results support the hypothesis that D_{1A} receptor activation plays a part in the sequencing of natural action. This conclusion has important implications for the understanding of the functional heterogeneity of dopamine receptor subtypes and of the aetiology of symptoms observed in patients with basal ganglia disease.

Introduction

Dopamine in the striatum has a clear influence over movement generation. Extensive loss of the neurotransmitter in the human brain from midbrain dopamine cell death produces Parkinson's disease characterized by the cardinal symptoms of severe akinesia, rigidity and tremor (Bernheimer & Hornykiewicz, 1965; Martin, 1967). However, the role of dopamine in motor control is complex and not limited to lower levels of motor function. Changes in dopamine neuron activity in non-human primates have been shown to be poorly correlated with simple reaching movements. Instead, many neurons are time-locked to the appearance or reception of liquid or food reward or associated conditioned stimuli paired with these rewards (Schultz *et al*., 1983; Ljungberg *et al*., 1991). On the other hand, striatal neurons that receive dopamine input have been shown to be related to movement generation (Delong *et al*., 1986) and also to higher aspects of movement such as sequential co-ordination (Aldridge *et al*., 1993; Cromwell & Berridge, 1996). Lesions of the dopamine system in animals alter higher motor processes such as movement sequencing, sensorimotor integration, motivational-motor linkage and motor learning (Beninger, 1983; Sabol *et al*., 1985; Schallert & Hall, 1988; Berridge, 1989; Brown & Robbins, 1989) in addition to simple motor control (Amalric & Koob, 1987; Schultz *et al*., 1989). These results indicate that dopamine modulates activity in the striatum and other areas of the brain involved in motor function and influences diverse aspects of behaviour.

One important characteristic of the dopamine system which may allow it to be multi-influential is its heterogeneous receptor family. There are five dopamine receptor subtypes (Sibley & Monsma, 1992), and recent studies have shown that there is potential for different molecular as well as behavioural outcomes after specific subtype activation (Stoof & Kebabian, 1984; Starr & Starr, 1986; Fletcher & Starr, 1987; Amalric *et al*., 1993). When D_1 receptors are selectively activated in rodents, a reliable set of behaviours is induced (Molloy & Waddington, 1984; Waddington *et al*., 1986). One of the most consistent behaviours observed is grooming.

Rodent auto-grooming consists of many different movements and movement sets. There are long periods of flexible grooming interposed

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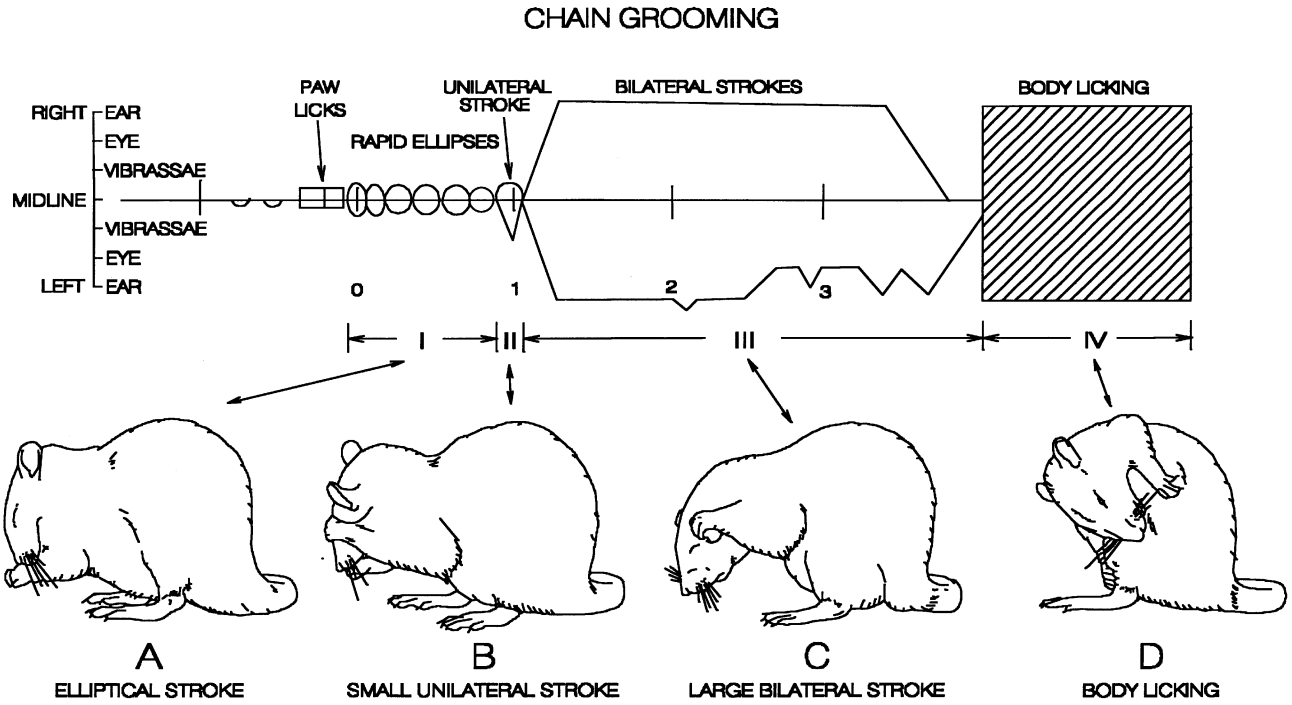

FIG. 1. The 'syntactic grooming chain' of rodents as shown in the rat. The chain has been observed in many rodent species including rats, hamsters, gerbils, squirrels, mice and guinea-pigs (Berridge, 1990). A choreographic transcription of a prototypical chain (above) shows the moment-by-moment trajectories of rapid ellipses of the paws around the snout and larger forepaw strokes. To read the choreographic depiction, time proceeds from left to right. The horizontal axis represents the position of the rat's mid-line and stroke trajectories are represented as deviations away from this mid-line (level of eye, the ear, etc.). Small rectangles represent paw licks and large rectangles represent body licking (adapted from Aldridge *et al*., 1993).

with shorter instances of reliable and highly stereotyped sequences of ordered actions. These relatively fixed serial order patterns of grooming actions have been termed 'syntactic grooming chains', and they organize up to 25 distinct movements into a predictable sequence (Fig. 1; Berridge *et al*., 1987). The sequential structure of syntactic grooming chains is sensitive to striatal lesions and to striatal dopamine depletion. These manipulations disrupt the serial order of the pattern without disrupting constituent movements (Berridge & Fentress, 1987; Berridge, 1989; Berridge & Whishaw, 1992).

Recently, homologous recombination techniques have been used to create mutant mice lacking functional D_{1A} receptors. Striatal function has been shown to be altered in these mutant mice (Drago *et al*., 1994; Levine *et al*., 1996a, Crawford *et al*., 1997) The goal of the present study was to examine the fixed grooming chain in the mutant mice to determine if functional D_{1A} receptors are important for efficient natural action sequencing.

Materials and methods

Animals

All procedures were completed in accordance with the *US Public Health Service Guide for Care and Use of Laboratory Animals*. Grooming behaviour was videotaped from both male and female controls (+/+; $n = 7$) and homozygous mutant mice littermates (–/–; $n = 9$) of at least 80 days of age. All animals ($n = 16$) were housed under standard conditions in groups of two to three on a 12 h light/dark cycle with food and water available ad libitum. As it has been shown that the mutant mice have lower body weights compared with littermate controls (Drago *et al*., 1994), cereal mash was given to the mice three times a week for supplemental feeding.

Genotyping mice

D_{1A} receptor knockout mice were generated from embryonic stem cells on which one of the D_{1A} receptor alleles was targeted *in vitro* by homologous recombination (Drago *et al*., 1994). Briefly, a targeting construct was designed (pKO.3) in which a neomycin phosphotransferase gene was inserted into a region of the D_{1A} receptor gene encoding the fifth transmembrane domain. In addition, 0.75 kb of gene sequence downstream of the insertion site was excised. The excised sequence encodes the third intracytoplasmic loop, the removal of which generates an inactive gene product. Positive clones were used to create chimeric mice. Chimeric males were mated with female C57BL/6 mice to create heterozygotes. Southern analysis was used to identify the genotype of mice (Drago *et al*., 1994).

Behavioural testing

Grooming bouts were videotaped during 10-min test sessions between 15.00 and 18.00 h. Grooming was elicited by lightly spraying the

dorsal side of the torso of the mouse with a water mist. Each mouse was placed in a clear plastic cage (30 × 20 cm) and filming was completed from the sides. The testing cage had a clear flat plastic top. The mouse was allowed to habituate to the testing cage for 5 min before its fur was sprayed. Testing sessions were repeated during subsequent days until a total of at least 10–12 min of grooming behaviour, cumulative across days, had been videotaped for each mouse (mean 9.5 days).

Grooming syntax

The serial organization of syntactic grooming chains arranges at least 15–25 forepaw strokes and licking actions into four consecutive sequential phases (Fig. 1) as follows.

Phase I

A concatenation of five to nine small, rapid bilateral forepaw strokes (ellipses) around the nose and mouth at a rate of 6–7 Hz. Ellipse stroke movements at this speed are extremely rare outside of syntactic chains. The concatenation of multiple ellipse strokes faster than 6 Hz virtually never occurs during non-chain grooming (Berridge, 1990). A fast series of phase I ellipse strokes thus serves as a marker for the initiation of syntactic chains.

Phase II

A short bout of one to four small or medium paw strokes along the mystacial vibrissae, usually performed by one unilateral paw or by both paws tracing asymmetric amplitudes.

Phase III

A repetitive series of three to 10 large bilaterally symmetrical strokes, which may extend behind the ears and most of the head.

Phase IV

A bout of body licking directed to the lateral and ventral torso.

Behavioural video analysis

All videotaping was completed at the Mental Retardation Research Center at the University of California at Los Angeles. Afterwards, videotapes were mailed to collaborators at the Department of Psychology at the University of Michigan to be analysed. Analysis was completed using slow motion viewing (frame by frame to one-tenth actual speed) by two trained raters who were blind to the genotype of the mouse. Scores were cross-checked across raters to ensure reliability. Tapes were scored in slow motion using a computer-aided event recording procedure and syntactic grooming chains were analysed frame-by-frame using a choreographic grooming notation system (Berridge *et al*., 1987). Grooming behaviour was analysed for the features listed below.

1 Time spent grooming per minute of observation.

2 Duration of grooming bouts, where a bout was defined as any continuous period of grooming that persisted without a 5-s pause.

3 Syntactic chain initiation. The number of grooming chains initiated per min spent grooming was tallied for each animal. This statistic identifies the propensity to engage in syntactic patterns. Chain initiation was defined as the occurrence of a full phase I: a bout of five to nine consecutive bilateral ellipses (small rapid strokes in which the paws trace a tight elliptical trajectory around the mouth) emitted at a rate of at least 6 Hz. To qualify as a syntactic chain initiation, phase I had to be followed immediately by either a phase II stroke, namely a unilateral stroke or an asymmetrical bilateral stroke over the vibrissae or a phase III stroke, namely a large amplitude forelimb stroke over the eyes or ears performed simultaneously with both paws.

4 Efficacy of syntactic completion. Once initiated, grooming chains were analysed for syntactic completion rates. A syntactically complete chain was defined as one that progressed through phases I, II, III and IV without interruption and within 5 s of phase I. The analysis was repeated using several criteria for completion, described below.

5 Microstructure of syntactic chains. The stroke-by-stroke structure of each syntactic chain was transcribed using a detailed choreographic notation system that depicts a moment-by-moment flow of paw trajectories and other grooming actions (Berridge & Fentress, 1987). The microstructure of the chain was analysed in terms of the number of forelimb strokes within phases I, II and III and the symmetry of these strokes. In addition, time intervals between chain components were analysed.

Statistical analysis

Differences between mean values for wild types and mutants were assessed with Student's *t*-tests for independent samples. Values for the *t* statistic and levels of significance are included in the text. In addition, data are presented as mean ± standard error in the text. Differences between the means of mutants and controls were considered statistically significant when $P < 0.05$.

Results

Overall grooming

It was generally noted that the D_{1A} deficient mice were not well groomed and that several of them had matted fur. Wild-type mice spent significantly more time grooming compared to D_{1A} mutant mice in terms of the percentage of time the animal spends grooming per minute of observation (wt = 43 ± 0.04%; mu = 31 ± 0.02%, $t = 2.87$, d.f. = 15, $P < 0.01$). Grooming bout length was also longer in the wild-type controls compared to the D_{1A} mutant mice (wt = 13.3 ± 1.8 s; mu = 7.6 ± 0.4 s/bout, $t = 3.44$, d.f. = 15, $P < 0.01$). There was no significant difference, however, between the mean number of grooming bouts (wt = 2.5 ± 0.3; mu = 2.34 ± 0.1; $t = 0.58$, d.f. = 15). The difference in time spent grooming seems attributable to shorter grooming bout durations in the mutant mice and not to the number of grooming series initiated.

Chain initiation

The initiation of the fixed action series of the grooming chain was examined separately. Despite their reduced grooming time and bout duration, the mutant mice initiated syntactic grooming chains more often per time spent grooming than the wild-type controls (wt = 0.04 ± 0.007; mu = 0.08 ± 0.01, $t = 2.51$, d.f. = 14, $P < 0.05$). This result indicates that even though overall grooming time is lower in mutant mice, the ability to *begin* syntactic grooming sequences remained primarily intact.

Syntactic efficacy: chain completion rates

Mice lacking the D_{1A} receptor had different numbers of complete and incomplete grooming chains. As shown in Fig. 2, mutant mice had a lower number of complete perfect chains compared with controls, and they also had a significantly higher number of incomplete grooming chains compared with controls (Fig. 2; wt = 11.5 ± 4.06%; mu = 29 ± 4.7%, $t = 2.73$, d.f. = 14, $P < 0.05$). Both controls and mutants appeared to have alterations in the grooming chain compared with previous observations of outbred mice strains (Berridge, 1990).

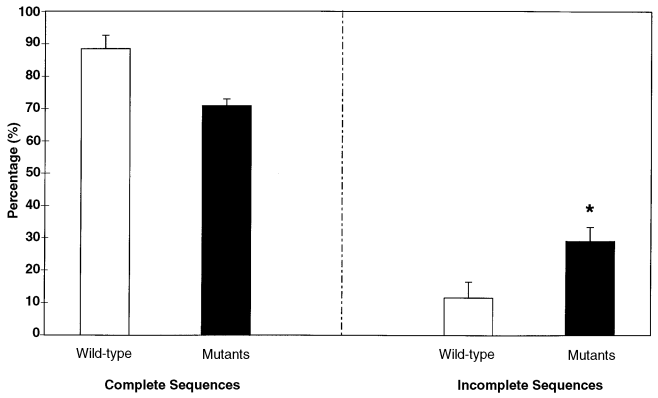

FIG. 2. Rates of syntactic completion for grooming chains. Mutant mice had a lower number of complete sequences (left side) and a significantly higher number of incomplete grooming sequences (right side).

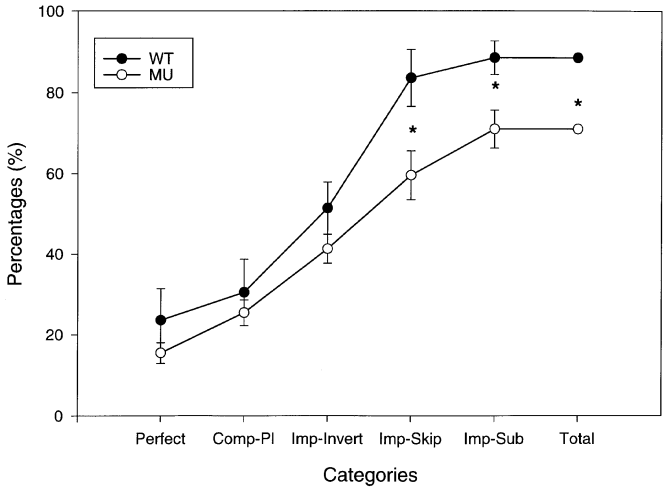

FIG. 3. Additive effect of completion subtypes. Mutant mice had a significant decrease in the percentage completion rate after different completion subtypes were used to categorize grooming chains. Both controls and mutants showed chains of the different categories but mutants showed a lower completion rate in each subtype. This difference was significant for the imperfect categories of skip and substitution as well as for the total cumulative percentage rate which combined the totals from each subtype. See Results section for a description of the different categories. Comp-PL = completion with paw licking, Imp-Invert = Imperfect Inversion Chain, Imp-Skip = Imperfect Skip Chain, and Imp-Sub = Imperfect Substitution Chain.

In an attempt to consolidate all chain forms, different completion subtypes were used to categorize the various patterns. These subtypes included: (i) 'imperfect substitution' completion occurs when the final phase IV component of body licking is replaced with paw licking (which does not require a major shift of balance or of the position of the head); (ii) 'imperfect inversion' completion occurs when two phases are sequentially reversed, but the chain is otherwise syntactically correct (e.g. I–III–II–IV or, more commonly, I–II–IV–III); (iii) 'imperfect skip' completion occurs when a chain lacked a particular phase but was otherwise syntactically correct (e.g. I–III–IV or I–II–IV); (iv) 'imperfect intrusion' completion occurs when an additional movement is injected during the chain, but the pattern continues afterward to completion. For each of these alterations, the animal performed the sequence to some form of phase IV (paw or body licking or attempted licking). Incomplete chains, by contrast, were those which, once initiated, never progressed fully to any form of phase IV licking but instead ended with either a return to flexible grooming or a transfer to another behavioural repertoire (e.g. walking) or a switch to a resting state. Mutant mice lacking D_{1A} receptors had a lower completion percentage in all subtype categories (Fig. 3). The greatest difference was observed in the 'imperfect substitution' and 'imperfect skip' subtypes ($t = 2.73$, d.f. = 14, $P < 0.05$ for both). When subtypes were combined into a single cumulative syntactic completion score, mutants had significantly lower numbers of ordered action sequences (Fig. 3; wt = 88.5 ± 4%; mu = 71 ± 4.5%, $t = 2.73$, d.f. = 14, $P < 0.05$). In other words, the mutant mice did not simply shift from perfect syntactic completion to some other form of imperfect completion. Instead, they were less likely to complete chains syntactically in any way. Overall, these results suggest that the mutant mice lacking D_{1A} receptors have an impairment in action sequencing.

Microstructure of syntactic chains

The microstructure of the grooming chain was compared across the two groups using choreograph transcriptions of chains emitted by individual mice to reveal details of component movements (Fig. 4). Differences were noted in the number of movements contained in particular phases of the chain. Mutant mice actually performed more ellipse-shaped strokes around the nose and mouth during phase I compared with the wild-type controls (mu = 10.25 ± 0.7; wt = 7.8 ± 0.5 ellipses, $t = 2.70$ d.f. = 15, $P < 0.05$), and had a marginally faster rate of ellipse stroke emission (mu = 10 ± 0.4 strokes/s; wt = 9.2 ± 0.4 strokes/s, $t = 0.6$, d.f. = 29). Thus, the early phase of syntactic chains by mutant mice may be more intense than wild-type control mice. However, D_{1A} deficient mutant mice performed fewer large amplitude forelimb strokes during the later phase III of the grooming chain (mu = 1.7 ± 0.18; wt = 2.8 ± 0.3 strokes; $t = 3.25$, d.f. = 38, $P < 0.01$). These results are consistent with the conclusion that mutant mice fail to maintain aspects of the sequential pattern during later phases of syntactic chains, leading to a failure to complete the sequence properly. For both groups, certain shared microstructural properties were noted. These included a high likelihood that when a 'skip' completion was performed it was most likely to involve phase III and when an 'inverted' completion was performed, phase III was also included on most occasions.

Discussion

The creation of transgenic mutant animals enables one to alter the synthesis of a specific genome product and identify the functional consequences. The present results show that a behavioural consequence of selectively removing the D_{1A} receptor in mice is an impairment of action sequencing, exemplified by the inability to complete syntactic grooming chains. A simple change in movement generation does not seem to be the cause of the alteration of action sequencing, as all of the individual movement types were observed in mutant mice, and they actually generated some movement components more energetically than did wild-type controls (e.g. phase I ellipse strokes). Nor were the mutants impaired in initiating the beginning of a serial pattern, as they began syntactic chain patterns more frequently than controls. Instead they appeared less able to follow the serial order pattern to its final stage, losing the sequential phase order as the chain progressed. They were deficient at carrying the serial pattern through to completion. This specific dysfunction of action sequencing may not signify that all action programming is altered, but it shows at least that a class of sequencing operations relevant to some species-specific natural sequences are affected.

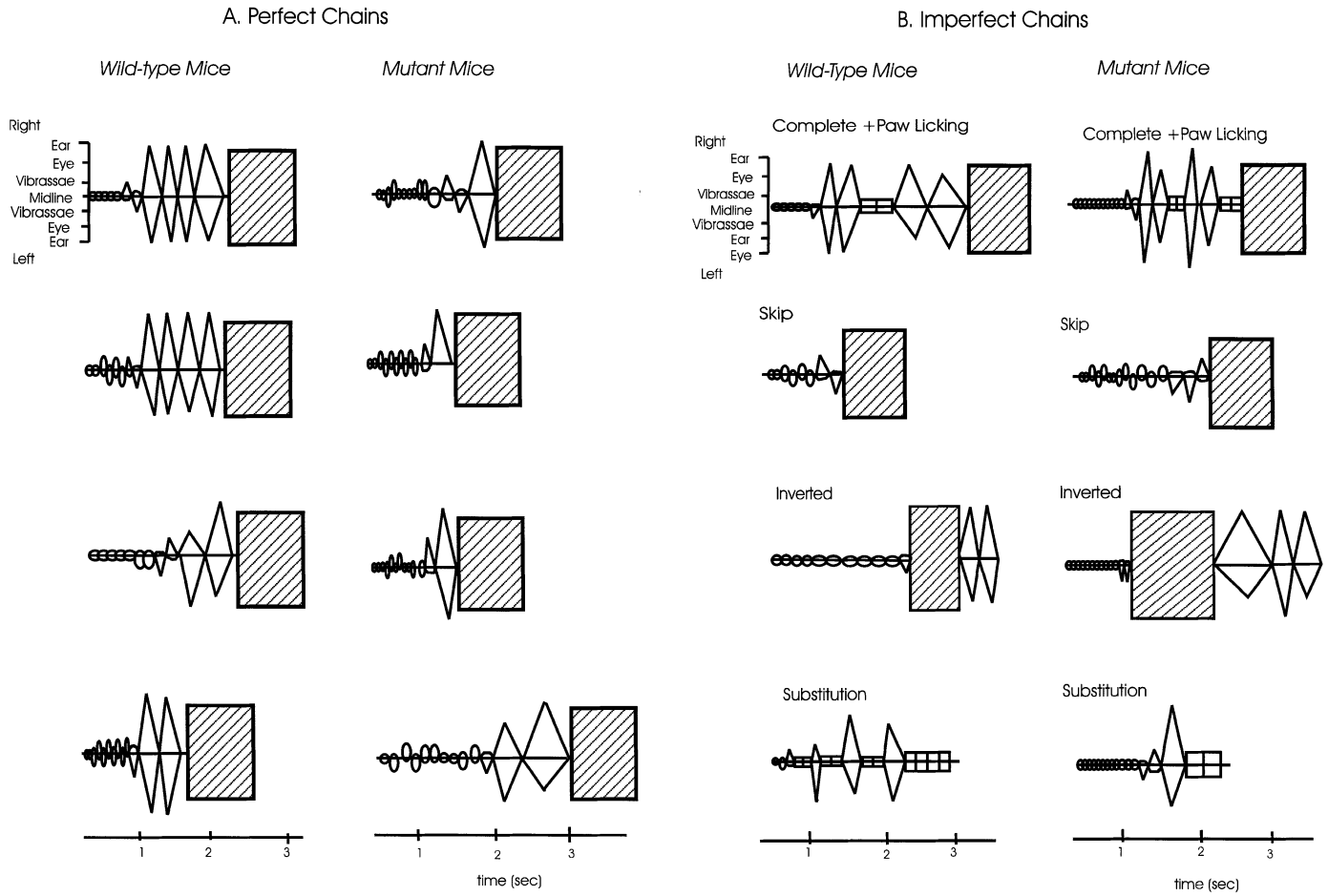

FIG. 4. Examples of notated chains from mutants and controls. Movements are notated along the horizontal axis. Small circles = ellipses, lines drawn above the axis denote forepaw movements around the face and the rectangles denote either paw licking (small) or body licking (large). These drawings depict a 'snapshot' of the representative movements of the animals from the two groups. Perfect chains were observed in both groups (A). Mutants showed a greater number of ellipse strokes and a fewer number of phase III strokes in these chains. Imperfect chains (for definition see Methods) were also observed in both groups (B) but the frequency was higher in mutants and the ability for completion of imperfect chains was less for each imperfect subtype in the mutant group.

There is previous evidence which suggests these animals may have difficulties in co-ordinating goal-directed action. It has been observed that D_{1A} knockout mice have significantly smaller body weights (Drago *et al*., 1994; Xu *et al*., 1994) which may signify a problem with movements which lead to successful eating such as forepaw grasping, forelimb movements or mouth movements. As the mice begin to partially regain weight after soft, cereal mash is offered, then the problem seems more likely to be attributed to difficulties in manipulating hard chow pellets and not with alterations in their motivation to eat. In addition, a drastic decrease in exploratory rearing has been observed in these mice (Drago *et al*., 1994). Rearing is a difficult movement of exploration in terms of the complexity of postural adjustments, and it may be highly sensitive to a sequential breakdown.

D_1 receptors, action sequencing and striatum

Bilateral lesions to a specific area of the rostral dorsolateral striatum produced sequential impairment of syntactic grooming chains in the rat (Cromwell & Berridge, 1996). The sequence completion deficit produced in rats by neostriatal lesions was similar to that observed in these transgenic mice. Neurons in this same striatal region respond electrophysiologically to sequential aspects of grooming during syntactic chains (Aldridge *et al*., 1993; Aldridge & Berridge, 1997). Bilateral lesions to dorsomedial, ventromedial or ventrolateral neostriatum or to nucleus accumbens did not impair sequential organization of syntactic grooming chains in rats, even though they produced other deficits. In addition, lesions of different cortical areas or cerebellum did not impair the sequential organization of syntactic grooming chains, suggesting that sequential organization is an intrinsic function of the anterior dorsolateral striatum in rodents (Berridge & Whishaw, 1992). This rostral dorsolateral region contains high numbers of D_1 receptors (Beckstead *et al*., 1988; Mansour *et al*., 1991) and it is quite plausible that D_1 receptor modulation of striatal neuron activity is important in producing efficient behavioural sequencing.

Although controversial, several studies have found D_1 receptors primarily on GABAergic medium spiny neurons which project to the internal segment of the globus pallidus (entopeduncular nucleus in the rat) or substantia nigra pars reticulata (direct pathway). By contrast, D_2 containing neurons project mainly to the external segment of the globus pallidus (indirect pathway) (Gerfen *et al*., 1990). This partial segregation of DA receptor subtypes could allow for isolatable functional influences within discrete components of basal ganglia circuitry. Lesions within the indirect pathway in rats (globus pallidus)

do not produce a sequential deficit in grooming syntax but produce an alteration in overall grooming activity (Cromwell & Berridge, 1996). The effects of lesions of the entopeduncular nucleus, the output of the direct pathway, upon the grooming chain have not yet been examined. The two pathways are also distinguished by the different neurochemical composition of their projection neurons. Neurons of the direct pathway which express D_1 receptors have been shown to colocalize substance P (Gerfen *et al*., 1990). Injections of D_1 agonists increase the expression of substance P mRNA (Gerfen *et al*., 1990). This link between D_1 receptors and substance P may be important for the co-ordination of action sequences. Several studies have shown that intracerebral injection of substance P elicits grooming in rats (Van Wimersma & Maigret, 1988; Ravard *et al*., 1994; Stoessl *et al*., 1995) and D_1 receptor antagonists inhibit grooming induced by substance P (Stoessl *et al*., 1995).

Additionally, D_1 receptor activation has been shown to enhance NMDA mediated responses of striatal neurons (Cepeda *et al*., 1993; Levine *et al*., 1996a). When the mutant mice were analysed in a previous study, the D_1 mediated enhancement of NMDA was found to be markedly reduced (Levine *et al*., 1996b). The D_1/NMDA interaction could play a part in the sequencing of natural action. When NMDA antagonists are pre-administered (CGP 43487 or MK-801) an inhibition of D_1 agonist-induced grooming was observed (Dall'Olio *et al*., 1996). This evidence *in toto* suggests that the critical intrinsic processing mechanisms within the striatum which lead to efficient motor sequencing could encompass D_1 modulation of the direct pathway GABAergic projection neurons (which coexpress substance P) as well as modulation of cortical glutamate input via NMDA receptors into the region.

D_1 receptors, action sequencing and basal ganglia disorders

The type of movement impairments seen in Parkinson's disease range from problems with movement generation to higher-level movement impairments including sequence disruption (Marsden, 1984). Patients have special difficulty completing sets of heterogeneous movements in the correct order (Talland & Schwab, 1964; Horne, 1973; Harrington & Haaland, 1991). The efficacy of D_1 agonists upon these sequencing deficits has not been studied in detail. In general, the administration of D_1 agonists to Parkinson's patients has led to mixed results including either a noted improvement in motor symptoms, especially tremor (Emre *et al*., 1992) or no change in motor severity score (Braun *et al*., 1987). Most current D_1 agonists show a lack of sufficient receptor selectivity and are rapidly removed from the local neuron environment which makes them imperfect candidates for pharmacotherapy. Recently, a D_1 receptor agonist with greater selectivity, A-86929, has been shown to be efficacious with repeated treatments in both rodent and primate models of Parkinson's disease (Asin *et al*., 1997). This result suggests that D_1 receptor stimulation, if pharmacologically reliable, can aid in treating symptoms of the disease.

Action sequences are altered in other basal ganglia diseases. Involuntary movements are expressed out of sequence in Huntington's disease (HD), Tourette's syndrome and ballism (Denny-Brown, 1962). Post-mortem analysis of striatal tissue from patients with HD have revealed a significant decrease in D_1 receptor number in the early stages of the disease (Richfield *et al*., 1991; Sedvall *et al*., 1994; Tirjanski *et al*., 1995) and a decoupling of the D_1 receptor from the guanine nucleotide binding protein Gs (De Keyser *et al*., 1989). In addition, substance P has been shown to be depleted in the striatum of HD patients (Kowall *et al*., 1993). It seems that a functional alteration in the D_1 expressing striatal projection neurons could lead to choreiform movements. This functional breakdown may be enhanced by additional circuitry re-wiring and damage to striatal neurons projecting to the lateral globus pallidus (Albin *et al*., 1990). It is only after significant loss of the D_1 containing striatal projection neurons to the internal segment of the globus pallidus that rigid/akinetic symptoms of HD commence (Albin *et al*., 1990). The findings of these clinical reports reinforce the idea that D_1 receptor activation makes an important contribution to motor sequencing.

Conclusions

Our results support the conclusion that D_1 receptor activation influences the sequencing of motor acts. The lack of the D_{1A} receptor leads not simply to an impairment in movement generation, but independently to a disruption of the sequential integrity of serially ordered patterns of movement. The basal ganglia system has been postulated to play a part in the sequencing of other phenomena in addition to movement (Marsden, 1982) and, recently, an hypothesis that this system is involved in the control of cognitive as well as motor pattern generators has been proposed (Graybiel, 1997). D_1 receptor activation in the striatum could be important in this non-motor sequential processing. Evidence that specific D_1 receptor activation modulates memory fields in prefrontal cortex supports the idea that this receptor subtype is involved in cognitive processing (Sawaguchi & Goldman-Rakic, 1994; Williams & Goldman-Rakic, 1995) and extending this involvement so that it can include action-orientated cognition may depend upon the recruitment of a D_1 receptor mediated influence within the basal ganglia system**.**

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