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Preface

It is our pleasure to present the Proceedings of the 16th International Congress on Parkinson's Disease (PD) and Related Disorders (16th ICPD) which took place in Berlin from June 5–9, 2005. This congress was the most successful congress ever with more than 3500 participants in the roaring German capital, consisting of an innovative program and with emphasis on bringing basic and clinical scientists together. Special attention has was paid in inviting young scientists. Therefore, the major aspect of scientific sessions was to identify young and up coming individuals in the field, with novel approaches to PD and novel models as a whole. The congress gave us the opportunity to present Germany and its capital after the burden of recent history in the new light of a reunified and peaceful country. We have succeeded in presenting the country as an important part of Europe and as a country of arts, architecture and renewal. The Congress attracted new friends from more than 75 countries worldwide. For this reason, we are most thankful to the World Federation of Neurology (WFN), Research Group on Parkinsonism and Related Disorders (RGPD), chaired by Professor Donald Calne for bringing this congress to Germany!

The Congress had many highlights with lectures covering all the major fields in PD and Related Disorders. The opening ceremony was highlighted by the inspiring presentation of Nobel Laureate Paul Greengard who lectured on dopamine-related signalling pathways in the brain, followed by the welcome addresses by Professor Riederer, President of the 16th ICPD, Professor Calne, President of the WFN-RGPD, Dr. Slewett, President emeritus of the National Parkinson Foundation, Miami, USA (NPF), Professor Kimura, President WFN, Professor Reichmann, President German Parkinson Society and Professor Einhäupl, Chairman of the Germany Science Council. The speeches were followed by a musical interlude of the ''Sunday Night Orchestra'' and the award ceremony of the WFN Research Committee on Parkinsonism and Related Disorders. The welcome reception presented typical German dishes and drinks.

In total the congress included 4 plenary lectures, 20 symposia, 6 hot topics, 4 video sessions, 1 workshop with demonstration, 29 educational seminars, more than 600 posters which were presented throughout the congress, 44 guided poster tours, 4 poster symposia, and 14 satellite symposia.

There were many scientific highlights and this proceeding intends to give a representative overview of congress programme. In this preface we are only able to give a glimpse of the outstanding lectures and scientific events during the 5 days.

The congress started with a satellite symposium on the significance of neuromelanin in the human brain. This symposium was dedicated to Prof. Youdim on the occasion of his 65th birthday. These contributions are published separately in a Special Issue of the Journal of Neural Transmission. Professor Carlsson, 2000 Nobel Laureate, spent significant time at the congress site and was often seen discussing topics of mutual interest with congress participant's. There was an interesting new study presented by Professor Deuschl, Kiel, in which he demonstrates that deep brain stimulation results in even better outcome of motor function than regular medication. For this reason, he advocated earlier use of deep brain stimulation in PD. New medications were discussed in detail both in the plenary lectures and satellites and new drugs such as rasagiline, the new MAO-B-inhibitor and rotigotine, the new dermal patch, were discussed in detail. There were satellite meetings on apomorphine, COMT-inhibitors, levodopa, spheramine (a new promising cell therapy for the treatment of PD in the advanced stage), dopamine transporter scanning, dopamine agonists such as pramipexole, ropinirole and cabergoline, adenosine antagonists, restless legs, deep brain stimulation, botolinum toxine A, and the new lisuride dermal patch. All satellites were of highest quality and delivered valuable insights in present and new therapy of PD. Special lectures addressed the advent of gene therapy and stem cell therapy, although it is apparent that there is still a long way to go until this therapy cab be safe and affordable for many PD patients longing for disease modifying treatment.

Professors Schapira and Olanow gave an overview on the ever contradictory aspects of neuroprotection. While neuroprotection is generally accepted in animal models and cell culture, there is still discussion on whether SPECT- and PET-analyses and the delayed start design, as employed in the rasagiline study indicated neuroprotection in man. For neuroprotection to be successful earlier diagnosis of PD is mandatory. For this reason, groups from Amsterdam, Dresden, Tübingen and Würzburg are working on early diagnosis procedures such as olfactory tests, parenchymal sonography, REM sleep analyses, and biochemical markers.

There were lectures on treatment of PD and many on genetic abnormalities causing PD, mitochondrial abnormalities and other disturbances of cell function which lead to dopaminergic cell death.

The other major aspect of the scientific session was the field of basic neuroscience to illuminate our current understanding of how neurons die in sporadic and familial PD. This included symposia on development of midbrain dopaminergic neurons, the role of iron in neurodegeneration, and the progress on genetics and proteomics and the concept of developing novel multifunctional neuroprotective drugs for such a complex disease.

Twenty nine educational seminars covered the most important topics and problems in clinical science bringing theory to practice and treatment strategies.

The guided poster tours allowed exchange of scientific ideas and shed light on new findings in etiology, diagnosis and treatment of PD and related disorders.

A special highlight of the Congress was the Art Exhibition, demonstrating the creativity of our patients with movement disorders. This exhibition was organized by the German Parkinson's lay organisation as well as by the Austrian lay organisation. Professor Maurer, Frankfurt, presented Art from an Alzheimer's patient, the Carolus Horn Exhibition, which impressively demonstrated change in the way to paint during a dementive process.

Another highlight was the Medical Historical Exhibition which was organised by Dr. Ch. Riederer, Würzburg, which focused on the history of the treatment of PD and emphasized the Berlin contributions by H. Lewy, W. v. Humboldt, R. Hassler and others.

A special tribute was paid to Melvin Yahr who sadly passed away in early 2005 shortly before this Congress. He was greatly missed.

Due to generous educational grants from the industry the organizers were able to honour outstanding scientists and clinicians, Toshiharu Nagatsu, Yoshikuni Mizuno, Japan (Award of the WFN Research Group on Parkinsonism and Related Disorders), Saskia Biskup, Germany and Andrew B. Singleton, USA (16^{th} ICPD Junior Research Award), Jonathan Brodie, Canada and Alan Crossman, UK (Merck KGaA Dyskinesia Research Award). GE Healthcare sponsored the 16^{th} ICPD Senior Researcher Award given to Silvia Mandel, Israel and Vincenzo Bonifati, The Netherlands. Both companies gave educational grants for the 12 Poster Prizes while the Melvin Yahr Foundation sponsored 26 Fellowships. In addition the congress made it possible to bring numerous young scientists to the congress by giving them financial support for travelling and accommodation.

The Senator Dr. Franz Burda Award presented by Helmut Lechner, Austria, and Franz Gerstenbrand, was given to Laszlo Vecsei, Hungary and Tino Battistin, Italy.

We thank all the participants who gave us their creative input to organize a World Congress on PD (as indicated in the First Announcement) which fulfilled the criteria of excellence and made the congress so successful. This was YOUR congress and which many of you influenced by letting us know your wishes and expectations. New concepts, formats and innovations, the active and constructive cooperation by the participating industry and the lay organisations made all this possible. This can measured by the numerous complimentary letters and emails we have received since then and we hope it sets the standards for future meetings! By doing all this we tried to come close to our milestone ''Present and Future Perspectives of Parkinson's Syndrome''.

Our special thanks go to CPO Hanser Congress Organisation, the programme committee and the WFN Research Group which all worked so hard to make this Congress so successful.

Finally the congress proceedings are published and we thank all those who contributed to this volume. Special thanks go to Springer Verlag, Vienna, New York for their efficient and splendid ability in being able to publish the proceeding so rapidly.

Peter Franz Riederer, Heinz Reichmann, Moussa Youdim, Manfred Gerlach

Würzburg, Dresden, Haifa, spring 2006

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Melvin Yahr (1917–2004). An appreciation

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Melvin Yahr (1917–2004)

I am honoured yet somewhat wary in being invited to write an appreciation of Melvin David Yahr. Can an outsider, a non-neurologist and a non-American, really grasp his contribution to movement disorder clinical practice, to the specialty of neurology, and to the larger world of Medicine? In so far as Melvin Yahr's importance extended beyond the borders of Neurology into all corners of the world, the answer is, perhaps, yes. Given such a long period of consistent and extensive activity (first paper in Journal of Pediatrics in 1944, 357th in 2003), much of the customary academic and professional rivalry and anguish, well described by Hornykiewicz (2004), will be unknown to an outsider and perhaps is better left that way until some future disinterested biographer intervenes. Here follow brief comments on some of his papers.

Duvoisin et al. (1963) give an insight into some 1960s thinking. Yahr and his colleagues studied a clinical sample from Columbia-Presbyterian Medical Center (225 subjects attending in 1962 of whom 195 had classical paralysis agitans) and refuted authors who asserted that, with the passing of the post-encephalitic cohort, Parkinsonism would largely disappear [by 1980] . . . thereafter constituting a numerically insignificant disease entity.

Melvin Yahr (Yahr et al., 1969) was important in those early years showing the efficacy of L-dopa (from Birkmayer and Hornykiewicz, 1961 onwards) and affirming that enough L-dopa would produce and sustain clinical response. (Hornykiewicz, 2004 engagingly and courageously records the chronology and conflict of those papers and their authors.) In a placebo controlled, double blinded study, with careful evaluation (more later about the Scale used for evaluation), 60 subjects, 56 with Parkinson's Disease, aged 44–78 years of at least 3 years duration and followed for 4 to 13 months, were given 750 mg to 1 gram of L-dopa 3 to 5 times daily. All these patients had been hospitalized for the study – those were the days! After initial symptomatic improvement, objectively there was 'renewed ability to perform simple movements which had been lost for several years, such as turning over in bed or rising from a chair'. They noted that some subjects did not reach ultimate functional improvement until treated for 3 to 4 months. Abrupt cessation of the drug led to loss of effect in the ensuing week and restoration took at least a further week.

Younger clinicians will have no memory of the excitement produced when L-dopa was introduced (in today's parlance, ''Awakenings'' is a 'must-read'). It is in the same league as witnessing the original clinical

response to penicillin (Fletcher, 1984) or the present writer's joy as an intern at the effectiveness of oral diuretics replacing parenteral mercurials.

In his 1970 presidential address to the American Neurological Association's 95th Annual General Meeting, Melvin Yahr began: ''I'm not a philosopher or historian, much less a prophet'' and then described ''Neurology's position in the present crisis in American medicine''. His analysis bears repetition and response even today. He bluntly asserted: ''the public is disaffected with the health care we are giving them'' ... the affluent complain about their waits to see physicians, the indigent complain they have no access to physicians. He warned that the false dichotomy of ''medical research'' *or* ''medical care'' ignored research as the catalyst for both clinical care and teaching. While recognizing the complementary nature of basic and applied research, he pleaded that their funding should not be in direct competition. Where he differs from many presidential addresses, which focus on the clinician and his (certainly *his* in 1970) preoccupations, is his dissection of the (American) health care delivery system ''which is about as unhealthy, uncaring and unsystematic a delivery system as one can imagine''. He emphasized the context: ''the senseless war in Vietnam, poverty, hunger, environmental pollution, divisions between the races, alienation of our young people. And somewhere in that group ... inadequate medical care.'' He challenged then and now: ''the large sums of money expended by our government on misguided military adventures should, instead, be serving the cause of human betterment and as physicians we have an obligation to say so''.

''100 years ago we were unable to exist with half slave half free, so we cannot now continue to exist with half our people barred from decent health care''. He envisaged developing ''a comprehensive health plan for all to which ability to pay will cease to be a barrier to participation''. He then applied these principles to neurological practice and training. He perceptively commented on: urban/rural practice (''the irresistible ambience of West Coast living'' – very pertinent for a former Winnipeg physician when read during a January sabbatical in Vancouver); the needed continuum of care required ''through the various phases of the many long-term diseases with which we are involved''; and he made an impassioned plea for ''one class of care – first class''. Other topics included telehealth (not his term) consultations, relevant CME in neurological matters for primary care physicians, and the relationship between the academic health centre and its medical hinterland. To this writer, this address was unexpectedly refreshing, revealing, and still relevant.

The Hoehn and Yahr Scale (1967)

It is a truism that Parkinson's Disease was and is a clinical diagnosis: there are no laboratory tests, no imaging techniques, no genetic markers to confirm the diagnosis. It is the clinician's decision. This judgment nicely combines the art and science of medicine but the first attempt to supply a scientific basis for this judgment appeared in Hoehn and Yahr (1967). This is Melvin Yahr's most famous paper (at least 2886 citations by mid-January, 2004) because it laid the foundation for *measuring* Parkinsonism.

The Hoehn and Yahr Scale appeared before the obligatory application of psychometric and clinimetric measures to clinical scaling, before sensitivity and specificity, before predictive values, before receiver operating curves and the rest of the scientific apparatus ensuring those twin pots of gold: validity and reliability (albeit tempered with simplicity, acceptability, accuracy, cost – Cochrane and Holland, 1971 – sensibility – Feinstein, 1987 – and responsiveness – Rockwood et al., 2003). The main objective of the paper was to determine the clinical variability, progression

and mortality of Parkinson's Disease given the then paucity of information about the natural history of the condition. This would subsequently give the background upon which to judge the effectiveness of the newly introduced L-dopa therapy.

Hoehn and Yahr reported on 802 subjects derived from a retrospective clinical sample of 856 patients diagnosed with paralysis agitans, Parkinson's Disease and Parkinsonism seen at the Columbia-Presbyterian Medical Center from 1949 to 1964. Nearly 85% had classic Parkinson's Disease and 13% had post-encephalitic associated Parkinsonism. This was the largest clinical sample hitherto studied. Two hundred and sixty three subjects attending in 1963–4 were examined more closely and it was from this subsample that the famous clinical stratification was derived. They found only 10% free of tremor at onset and incidentally note the continuing occasional clinical conundrum of Parkinsonism and essential tremor; 14% exhibited ''mild-to-moderate organic mental syndrome . . . usually characterized by recent memory defects and some impairment of judgment and insight''; 4% were ''moderately to severely depressed'' (no further details given).

They wisely point out that the presence of the classical signs of tremor, rigidity and akinesia varies with respect to disability – its presence and progress; hence the need to quantify this interaction of physical signs and functional consequences into clinical stages. Hoehn and Yahr recognized that these stages may not correlate with pathology but they claimed a clinimetric basis for ''reproducible assessments by independent examiners of the general functional level of the patient''.

Five clinical stages, ''based on the level of clinical disability'' were reported on 183 patients with ''primary parkinsonism'' (viz. Parkinson's Disease, paralysis agitans or idiopathic Parkinsonism) – a subset of the 263 'more closely examined'. They dichotomized these stages into: mildly affected (Stages 1–III) and severely affected (Stages IV–V).

Five clinical stages: degrees of disability

Stage I: unilateral involvement only, usually with minimal or no functional impairment.

Stage II: bilateral or midline involvement, without impairment of balance.

Stage III: first sign of impaired righting reflexes. This is evident by unsteadiness as the patient turns or is demonstrated when he is pushed from standing equilibrium with the feet together and the eyes closed. Functionally the patient is somewhat restricted in his activities but may have some work potential depending on the type of employment. Patients are usually capable of leading independent lives and their disability is mild to moderate.

Stage IV: fully developed, severely disabling disease; the patient is still able to walk and stand unassisted but is markedly incapacitated.

Stage V: confinement to bed or wheelchair unless aided.

It is unfair to criticize a 1967 paper in terms of current epidemiological standards (McDowell, 1996). Clinically derived scales (e.g. Rankin, 1957 for stroke rehabilitation) are still used inspite of academic strictures. Ramaker et al. (2002) in their recent comprehensive review of measuring Parkinson's Disease, regret that the Hoehn and Yahr Scale is frequently chosen ''as the gold standard for testing other scales'' because of its lack of psychometric and clinimetric properties – but at the time it emerged it was groundbreaking.

Melvin Yahr contributed to many major textbooks of Medicine, Neurology and Movement Disorders. In his 357 publications, themes included: amino acid biology, the

continuing relationship of central nervous system infection and Parkinsonism, autonomic nervous system failure with special attention to orthostatic hypotension, and every aspect of the drug management of Parkinson's Disease. His experience and expertise (in others not necessarily the same thing) were highly valued. No part of movement disorder neurology was untouched by his presence: as an explorer, quantifier, analyser, teacher and practitioner. An obituary by former students (Di Rocco and Werner, 2004) expresses the richness of his contribution to neurology and neurologists. He was an exemplar of successful ageing. Rejecting the curse of mandatory retirement, he continued his clinical and academic work into the last weeks of his life: he was the *compleat* physician.

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Melvin D. Yahr, 1917–2004. A personal recollection

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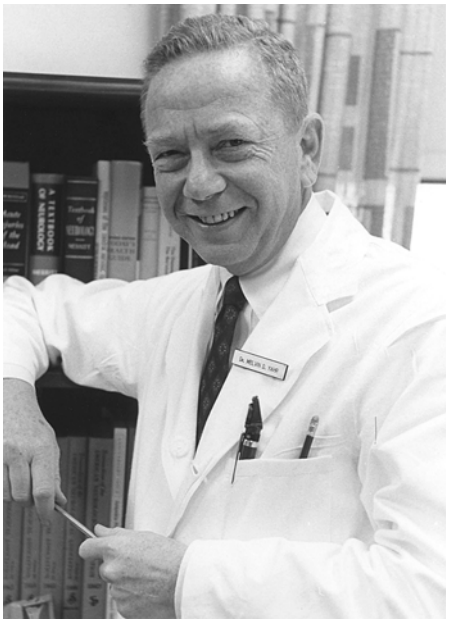

Melvin D. Yahr, one of the giants of 20th century neurology died on January 1st 2004, aged 87, of lung cancer, at his home in Scarsdale, New York. His was an intense and long life of uninterrupted scientific productivity. His first paper, on myasthenia gravis, was published in 1944 and his last one, of course on Parkinson's disease, appeared in press in 2005, sixty one years later. Born in 1917 in New York City, Yahr was the youngest of six children of immigrant parents. His family lived in Brooklyn where his father owned a bakery. He went to New York University School of Medicine and completed an internship and residency at Lenox Hill Hospital and Montefiore Hospital in New York City. As a student he played the clarinet in a jazz combo to earn extra money, but insisted that he was not a talented musician. Later, when questioned about the origin of the phenomenal musical talent of his daughters, he attributed all to his wife Felice, whom he married when she was a 23-year-old writer working at Fortune Magazine. Yahr served in the US army from 1944 to 1947 and was discharged with the rank of Major. Back in NY, he joined the faculty at Columbia University College of Physicians and Surgeons where he began his work as an academic neurologist. He had wide clinical interests

but after a few years he began focusing on Parkinson's disease. Building on the work of Carlsson, Hornykiewicz and Cotzias, in the 1960's Yahr conducted the first double blind randomized large clinical trials of Ldopa in the treatment of Parkinson's disease. The success and impact of this treatment was tremendous; patients were ''unfrozen'' from statue-like rigidity and brought back to life. In 1967, together with Peggy Hoehn, he devised a 5-stage scale, simplicity itself, to determine the severity of Parkinson disease. The Hoehn and Yahr rating scale is still the gold standard and levodopa remains the most widely used medication for the treatment of Parkinson's disease.

Melvin Yahr became H Houston Merritt professor of neurology at Columbia University before moving downtown, as he used to say, to Mount Sinai School of Medicine, where he become professor of neurology and chairman of the department. Yahr brought to Mount Sinai the country's first multidisciplinary center for research in Parkinson's disease and related disorders, a pioneering example of translational research. Under his leadership, basic scientists and clinical investigators working in close proximity, made significant contributions to the understanding and treatment of these disorders.

He chaired study sections for the National Institute of Neurological Communicative Disorders and Stroke, he was an adviser for the National Research Council, the National Academy of Sciences, and the New York City Board of Education. He was president of the American Board of Neurology and Psychiatry, the American Neurological Association, and the Association for Research in Nervous and Mental Diseases. He received many prizes and awards and was an honorary member of the British, French, Belgium and Argentine Neurological societies.

Melvin Yahr was an imposing presence. I first met him in 1982 during my neurology residency at Mount Sinai. He was 64, famous and at the top of his game. He had a low baritone voice and a very characteristic way of speaking that we all used to imitate. He was impeccably dressed and always wore a crisp shirt and tie under his white lab coat. And he smoked a pipe, an indispensable tool for the neurologist-detective of his generation.

Yahr was first and foremost a clinician; but believed strongly in basic research. He loved neurology and he got great satisfaction from his work. He was a superb teacher. I remember vividly Morning Reports as a senior neurology resident; every day of the week at 9 in the morning, after rounding the neurology ward, the senior residents went into his office in the 14th floor of the Annenberg Building, junior residents were not allowed. The 5 or 6 seniors sat in couches and chairs facing him who was sitting behind his desk, reclined backwards, almost always smoking a pipe. The curtains were usually lowered, so the room was dark. Many times we couldn't see his face because it was covered by the desk lamp and by a journal he was reading and holding in front of him. One could only see the smoke from his pipe coming up from behind the journal. We felt we were in front of the oracle. We presented each new patient trying to be brief and to the point. At the end of each patient's presentation we heard his voice saying: next! or some short comment. But sometimes it was different. He would put the journal down and ask a few more questions and then go through the differential diagnosis or focus on one particular aspect of the history and what it meant. For us it was magic, it all made sense when he explained it. He left us mesmerized and we walked out of his office full of ideas and imagining that we actually knew what we were all doing. Clinical neurology was an exciting job with Melvin Yahr.

Twice a week he also did ''Chief of Service Rounds.'' With all the residents and medical students sitting around him, he interrogated and examined a patient from the Neurology ward. With Melvin Yahr this was high theatre. He was a master performer.

Melvin Yahr was outspoken and blunt and was used to be in charge. He was not easily convinced (– of anything), and his most typical questions were – ''What do you want?'' to his students and ''What is it that you cannot do?'' to his patients. He was frequently gruff and stern but had a fine sense of humor and compassion.

Almost everything that is necessary for a neurological diagnosis is in the history, he used to say and he mostly stuck to that. Of course he used radiology and electrophysiology extensively, but he had a deep distrust for all forms of testing. He asked patients very clear questions and had the ability to make them talk and reveal information that nobody else seemed to have been able to obtain. He listened intently, rarely interrupting with his gaze locked on the patient. His neurological examinations were very focused brief and revealing: as residents, we entertained the possibility that Yahr could actually alter plantar responses in patients at will, and we believed that he always knew what he was going to find, as he never appeared surprised. He kept the tradition of clinical neurology training one on one, almost like an apprentice. Neurology was his passion. He was a methodical thinker, disciplined, focused and persistent.

Melvin Yahr did not believe in retirement. When he stepped down as chairman at Mount Sinai in 1992, his office was demolished, literally. I guess the powers to be thought he would have stayed there otherwise. Undeterred, he got a new office, and a new endowed chair remaining as active as ever.

He appreciated beauty, loved red wine and cognac. A favorite line of his was ''It's a racket!'' applied to a variety of senseless medical or everyday life schemes. He was a Democrat, which in the US, means liberal.

He is survived by Nancy his companion after the death of his wife Felice in 1992, and by 4 brilliant daughters, Carol an opera singer, Barbara, an orchestra conductor, Laura a pathologist and Nina a social worker, and 5 grandchildren.

Melvin Yahr died 200 years after James Parkinson. He would have pointed that out. Until the end Yahr remained intellectually vibrant. He was writing and seeing patients just a few weeks before his death. He will be missed.

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The discovery of dopamine deficiency in the parkinsonian brain

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Summary. This article gives a short historical account of the events and circumstances that led to the discovery of the occurrence of dopamine (DA) in the brain and its deficiency in Parkinson's disease (PD). Some important consequences, for both the basic science and the patient, of the work on DA in the PD brain are also highlighted.

Early opportunities

In 1951, Wilhelm Raab found a catecholamine (CA)-like substance in animal and human brain (Raab and Gigee, 1951). He knew that this CA was neither noradrenaline (NA) nor adrenaline; today, we know that it was, at least in part, dopamine (DA). Raab examined its regional distribution in the brain of humans, monkeys and some "larger animals", and found highest levels in the caudate nucleus. He found no changes of this CA in the caudate in 11 "psychotic" patients. He did not try to look for this compound in the caudate nucleus of patients with Parkinson's disease (PD).

In 1952, G. Weber analyzed brains of patients with PD, obtained postmortem, for cholinesterase activity (Weber, 1952). He found a reduction of the enzyme activity in the putamen, and hypothesized about the significance for PD. Had Weber known of Raab's study published the year before, he might have measured Raab's CA-like compound in his PD postmortem material. In his report, Weber does not refer to Raab's study.

In 1952–1954, Marthe Vogt performed her landmark study of the regional distribution of NA and adrenaline in the brain of the dog (Vogt, 1952, 1954). She isolated the amines from brain tissue extracts by paper chromatography and eluted the corresponding "spots" for (biological) assays. Marthe Vogt was well aware of Raab's work. However, for practical reasons, she did not stain the CA (with ferricyanide) on the chromatograms of regions that contained little NA, such as the caudate; thus she let pass the opportunity of detecting DA's presence in the brain and its striatal localisation.

Setting the stage for the DA/PD studies

In August 1957, Kathleen Montagu reported on the presence of DA, identified by paper chromatography, in the brain of several species, including a whole human brain (Montagu, 1957). In November 1957, Hans Weil-Malherbe confirmed this discovery and examined DA's intracellular distribution in the rabbit brain stem (Weil-Malherbe and Bone, 1957). Neither he, nor Montagu, offered any speculations on the physiological role of brain DA. At the same time as Weil-Malherbe, in November 1957, Arvid Carlsson observed that in naïve and reserpine treated animals "*3,4-dihydroxyphenylalanine caused*

central stimulation which was . . . markedly potentiated by iproniazid" (Carlsson et al., 1957). He concluded that the study "*supports the assumption that the effect of 3,4-dihydroxyphenylalanine was due to an amine formed from it"* – leaving the question of whether this amine was NA or DA, unconsidered. In the Fall of 1957, a few weeks before Carlsson's report, Peter Holtz published observations on, *inter alia*, L-dopa's central stimulant and "awakening" (from hexobarbital anesthesia) effects, and clearly suggested, apparently for the first time, that this could be due to the accumulation of "*the dopamine formed in the brain from L-dopa"* (Holtz et al., 1957). (Raab, in 1951, was the first to observe increased brain levels of his CA-like substance after i.p. L-dopa; but he does not mention any behavioral L-dopa effects [Raab and Gigge, 1951].)

Holtz's conclusion was soon confirmed in two biochemical studies. In February 1958, Carlsson reported that reserpine depleted, in addition to NA and serotonin, brain DA, and L-dopa replenished it while causing central excitation (Carlsson et al., 1958). In May 1958, Weil-Malherbe obtained, independently, the same biochemical results in a well documented study (Weil-Malherbe and Bone, 1958). Neither Carlsson nor Weil-Malherbe ventured any explicit statements about brain DA's possible physiological role or its involvement in the reserpine syndrome.

More than a year before these first brain DA studies, in the Fall of 1956, Blaschko had already proposed that DA – until then seen as being merely an intermediate in the biosynthesis of CA – had "*some regulating functions of its own which are not yet known"* (Blaschko, 1957). In early 1957, Hornykiewicz, in Blaschko's Oxford laboratory, tested this idea experimentally. He analyzed DA's vasodepressor action (in the guinea pig) and proved that DA had actions distinct from NA and adrenaline and thus qualified as a biologically active substance in its own right; L-dopa behaved exactly like DA (Hornykiewicz, 1958). In 1958, Hornykiewicz (now back in Vienna) examined (in the rat) the central actions of several substances, including the parkinsonism-inducing chlorpromazine and bulbocapnine, as well as cocaine and MAO inhibitors, and showed that only the latter affected (increased) the levels of brain DA (Holzer and Hornykiewicz, 1959).

Marthe Vogt, in her 1954 NA study in the dog brain, inferred NA's possible role in brain function from the amine's specific distribution pattern. In January 1959, Åke Bertler and Evald Rosengren, patterning themselves on Marthe Vogt's NA study, published a study, also in the dog, on the regional distribution of brain DA (Bertler and Rosengren, 1959a); a few weeks later, Isamu Sano reported on DA's regional distribution in the human brain (Sano et al., 1959) (followed by Bertler and Rosengren, 1959b). Both research groups found that DA was mostly concentrated in the nuclei of the basal ganglia, especially caudate and putamen. Bertler and Rosengren (1959a) concluded that their "*results favour*[ed] *the assumption that dopamine is connected with the function of the corpus striatum and thus with the control of movement"*; and Sano "*considered DA to function in the extrapyramidal system which regulates the central motoric function"* (Sano et al., 1959). Although Bertler and Rosengren pointed out DA's possible involvement in reserpine parkinsonism, neither they nor Sano suggested the possibility of striatal DA being directly involved in diseases of the basal ganglia.

DA is severely reduced in PD striatum

Several eyewitness accounts have recently been written about the historical events and consequences of the discovery of the DA deficiency in PD (Sourkes, 2000; Hornykiewicz, 2001a, b, 2002a, b).

Early in 1959, Hornykiewicz, aware of DA's localisation in the basal ganglia, started

a study on DA in postmortem brain of patients with PD and other basal ganglia disorders. He and his collaborator Herbert Ehringer analyzed the brains of 17 adult non-neurological controls, 6 brains of patients with basal ganglia disease of unknown etiology, 2 brains of Huntington's disease, and 6 Parkinson brains. Of the 14 cases with basal ganglia disease, only the 6 PD cases had a severe loss of DA in the caudate and putamen (Ehringer and Hornykiewicz, 1960). Ehringer and Hornykiewicz concluded that their observations "*could be regarded as comparable in significance* [for PD] *to the histological changes in substantia nigra"* . . . so that "*a particularly great importance would have to be attributed to dopamine's role in the pathophysiology and symptomatology of idiopathic Parkinson's disease"*. This discovery was published in December 1960. Ever since, it has provided a solid, rational basis for all the following research into the mechanisms, the causes, and new treatments of PD.

It is interesting to note that in none of the brain DA and/or L-dopa studies preceding the Ehringer and Hornykiewicz 1960 paper, is there any hint to be found that such a study should be done. The first such suggestion was made in an article from Montreal, submitted for publication end of November 1960, reporting on reduced urinary DA in PD patients. The authors concluded that future investigations should "*include analysis of the catecholamine content in the brains of patients who have died with basal ganglia disorders"*, so as to "*help determine whether the concentration of cerebral dopamine itself undergoes major changes"*. The article was published in May 1961; a "note added in proof" informed the readers that the suggested study has, in the meantime, been done (Barbeau et al., 1961).

The fact that the Montreal group quoted the paper from Vienna so soon after it was published on December 15, 1960, deserves a comment. This article was written in German and published in a German language journal. Theodore Sourkes, the leading biochemist of the Montreal group, must have read it almost immediately after it came out. He contacted Hornykiewicz about this article by letter dated February 10, 1961. For the Vienna discovery, there were, obviously, neither language nor information transfer barriers. This was opposite to what happened to a (lecture) overview article of Sano, published in Japanese in 1960. Independently from Hornykiewicz, Sano had analyzed the brain of a single PD patient, but was "*reluctant to speculate, from that single experience* [low putamen DA] *about the pathogenesis of Parkinson's disease"* (Sano, 1962). The publication remained unnoticed until it was recently reprinted in English translation (Sano, 2000).

The question arises: Why did none of the pioneers of the early brain DA research think of studying the PD brain? It appears that the main reason was their too exclusive preoccupation with the central effects of reserpine. This is surprizing because even then it was obvious that reserpine, like most pharmacological animal models, was not a perfect centrally acting drug; it depleted, to the same degree as DA, also the brain NA and serotonin, making a clear decision about the relative importance of these changes impossible. The exclusive "fixation" on reserpine made leading monoamine researchers of that period overlook the most obvious, that is, PD as the ultimate "brain DA experiment of Nature".

Two practical consequences

Inaugurating the nigrostriatal DA pathway

When the DA deficiency in PD was discovered, nothing was known about DA's cellular localisation in the brain. In Huntington's disease, Ehringer and Hornykiewicz (1960) had found normal striatal DA. Since in Huntington's disease there is a severe loss of striatal neurons accompanied by marked gliosis, the normal striatal DA suggested that the amine was probably contained in terminals of fibre tracts originating outside the striatum. Rolf Hassler

had proved, back in 1938, that in PD, loss of the substantia nigra compacta neurons was the most consistent pathological change (Hassler, 1938). Thus, in 1962, Hornykiewicz started a study of the substantia nigra in 10 PD brains. The outcome of such a study was by no means certain. Hassler himself rejected the possibility of a nigro-striatal connection (see page 869 in: Jung and Hassler, 1960); and Derek Denny-Brown declared, in 1962, that "*we have presented reasons against the common assumption that lesions of the substantia nigra are responsible fo parkinsonism"* (Denny-Brown, 1962). In his study, Hornykiewicz found markedly reduced nigral DA, similar to the DA loss in the striatum. In the report published in 1963, Hornykiewicz concluded from his observation that "*on the other hand, cell loss in the* [PD] *substantia nigra could well be the cause of the dopamine deficit in the striatum"* (Hornykiewicz, 1963).

At the time of Hornykiewicz's DA/substantia nigra study, two research groups were already trying to tackle the question of brain DA's cellular localization. In Montreal, Poirier and Sourkes were using electrolytic brain lesions, in the primate; in Sweden, Fuxe, Dahlström (and others) were applying, in the rat, the just developed CA histofluorescence method. A year after Hornykiewicz published his study, each of the two research groups was able to report on the existence of a DA-containing nigrostriatal connection. Both groups referred, in their first publications, to Hornykiewicz's 1963 nigral DA study (Andén et al., 1964; Dahlström and Fuxe, 1964; Poirier and Sourkes, 1965). This contribution to the discovery of the nigrostriatal DA pathway had for Hornykiewicz yet another consequence. Several years later, Hassler wrote him a letter in which he expressed his candid opinion on the nigrostriatal DA pathway. He wrote: "*I believe that your interpretation of your observations does not agree with many known facts, this being so because you accept the American* [?!] *opinion about the direction of the nigrostriatal connections. I believe that all your observations can be equally well, or even better, explained by the striatonigral direction* [of that pathway]*"* (Hassler, 1967).

L-dopa for the PD patient

The discovery of the severe striatal DA deficiency in PD had also a far-reaching clinical consequence. Hornykiewicz immediately took the step "from brain homogenate to treatment" and asked the neurologist Walther Birkmayer to do clinical trials with i.v. L-dopa. After a delay of eight months, in July 1961, Birkmayer injected 50–150 mg L-dopa i.v. in 20 PD patients, most of them pretreated with an MAO inhibitor. The first report, published in November 1961, conveys, even today, the excitement about what since has been called "the dopamine miracle"; it reads as follows:

The effect of a single i.v. administration of L-dopa was, in short, a complete abolition or substantial relief of akinesia. Bed-ridden patients who were unable to sit up; patients who could not stand up when seated; and patients who when standing could not start walking, performed after L-dopa all these activities with ease. They walked around with normal associated movements and they even could run and jump. The voiceless, aphonic speech, blurred by pallilalia and unclear articulation, became forceful and clear as in a normal person. For short periods of time the patients were able to perform motor activities which could not be prompted to any comparable degree by any other known drug. (Birkmayer and Hornykiewicz, 1961).

Simultaneously with, and independently from, the trials in Vienna, Sourkes and Murphy, in Montreal, proposed to Barbeau a trial of oral L-dopa. They observed, with 200 mg L-dopa, an amelioration of rigidity that "*was of the order of 50 percent"* (Barbeau et al., 1962). Interestingly, Sano in his overview in 1960 also mentioned that he

had injected 200 mg L-dopa i.v. in two patients; however, he did not evaluate the effect clinically, being "*more interested in subjective complaints"* (Sano, 1962). Sano concluded that "*treatment with dopa has no practical value"* (Sano, 2000).

Today, especially thanks to Cotzias's introduction of the high dose oral treatment regimen (Cotzias et al., 1967), L-dopa is recognized as the most powerful drug available for PD. As Sourkes very aptly expressed it, the discovery of L-dopa "*proved to be the culmination of a century-and-a-half search for a treatment of Parkinson's disease"* (Sourkes, 2000).

Despite the unprecedented success, doubts were expressed about L-dopa's "miraculous" antiparkinson effect. Many neurologists suspected a placebo effect of the i.v. injected L-dopa, ignoring the fact that Birkmayer and Hornykiewicz (1962) had described, already in 1962, the ineffectiveness of i.v. injected compounds related to L-dopa, such as: D-dopa, 3-O-methyldopa, DA, D, L-dops, and also 5-HTP. This should have convinced the doubters that the L-dopa effect could not have been a placebo effect.

Especially counterproductive were various statements by some rather prominent brain scientists. Thus, some claimed that "*the actions of DOPA and DOPS* [the direct precursor of NA] *were similar"*, cautioning that "*dopamine can activate not only its own receptors* [in the brain], *but also those of noradrenaline, and vice versa"* (Carlsson, 1964, 1965); others felt that "*the effect of L-dopa was too complex to permit a conclusion about disturbances of the dopamine system in Parkinson's disease"* (Bertler and Rosengren, 1966), still others compressed all their doubts in the terse phrase that L-dopa "*was the right therapy for the wrong reason"* (Ward, 1970; Jasper, 1970); and, finally, there was the statement that "*since L-dopa floods the brain with dopamine, to relate its* [antiparkinson] *effects to the natural function of dopamine neurons may be erroneous"* (Vogt, 1973). These and similar critical statements diminished the status of L-dopa as a specific DA replacing agent and put in doubt the very concept of DA replacement in PD.

Viewed against the background of the initial skepticism, today's opinion has substantially changed, as reflected, for instance, in a recent "Editorial":

The identification of the dopaminergic deficit in Parkinson's disease and the development of dopamine replacement therapy by Hornykiewicz and his contemporaries profoundly influenced research into Parkinson's disease, and perhaps even all neurological disorders. This is especially true for Alzheimer's disease, in which current cholinergic therapy is the intellectual heir of dopamine replacement therapy for Parkinson's disease. (Hardy and Langston, 2004).

Thus has theoretically based research led, in an amazingly straight line, to very practical results. As Immanuel Kant, that eminent philosopher of the Age of Enlightenment, put it some 200 years ago: "There is nothing more practical than a sound theory".

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Synchronizing activity of basal ganglia and pathophysiology of Parkinson's disease

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Summary. Early physiological studies emphasized changes in the discharge rate of basal ganglia in the pathophysiology of Parkinson's disease (PD), whereas recent studies stressed the role of the abnormal oscillatory activity and neuronal synchronization of pallidal cells. However, human observations cast doubt on the synchronization hypothesis since increased synchronization may be an epi-phenomenon of the tremor or of independent oscillators with similar frequency. Here, we show that modern actor/critic models of the basal ganglia predict the emergence of synchronized activity in PD and that significant non-oscillatory and oscillatory correlations are found in MPTP primates. We conclude that the normal fluctuation of basal ganglia dopamine levels combined with local cortico-striatal learning rules lead to non-correlated activity in the pallidum. Dopamine depletion, as in PD, results in correlated pallidal activity, and reduced information capacity. We therefore suggest that future deep brain stimulation (DBS) algorithms may be improved by desynchronizing pallidal activity.

Introduction: The computational roles of the basal ganglia and dopamine

Modeling of the basal ganglia has played a major role in our understanding of the physiology and pathophysiology of this elusive group of nuclei. These models have undergone evolutionary and revolutionary changes over the last twenty years, as ongoing research in the fields of anatomy, physiology and biochemistry of these nuclei has yielded new information. Early models dealt with a single pathway through the basal ganglia nuclei (cortex-striatum-internal segment of the globus pallidus; GPi) and focused on the nature of the processing performed within it, convergence of information vs. parallel processing of information. Later, the dual (direct and indirect) pathway model (Albin et al., 1989) characterized the inter-nuclei interaction as multiple pathways while maintaining a simplistic scalar representation of the nuclei themselves. The dual pathway of the basal ganglia networks emphasized changes in the discharge rates of basal ganglia neurons. The model predicts that in the dopamine depleted Parkinsonian state firing rates in the external segment of the globus pallidus (GPe) are reduced, whereas cells in the internal segment (GPi) and the subthalamic nucleus (STN) display increased firing rates (Miller and DeLong, 1987; Bergman et al., 1994). This model resulted in a clinical breakthrough by providing key insights into the behavior of these nuclei in hypo- and hyper-kinetic movement disorders, and lead

to subsequent findings showing that inactivation of STN and GPi can improve the motor symptoms in Parkinsonian animals (Bergman et al., 1990) and human patients. Finally, in line with the model predictions many studies have demonstrated reversed trends of pallidal discharge rates in response to dopamine replacement therapy (DRT) in both human patients and primates (e.g. Heimer et al., 2002). The next generation of models elaborated the intra-nuclei interactions and focused on the role of the basal ganglia in action selection and sequence generation which form the most current consensus regarding basal ganglia function in both normal and pathological conditions (Mink, 1996).

The dual pathway rate and the action-selection models represent the most common delineation of the basal ganglia functional anatomy and physiology. Nevertheless, new findings challenge these models. Thus, several primate studies have failed to find the expected significant changes of firing rates in MPTP monkeys. Similarly, biochemical and metabolic studies indicate that GPe activity does not change in Parkinsonism. Whereas the rate model strongly predicts that the enhanced GPi inhibitory output in Parkinsonism should reduce thalamic and motor cortex firing rates, several studies in dopamine-depleted primates have shown no change in spontaneous thalamic and motor cortical firing rates (e.g. Goldberg et al., 2002). Finally, both the dual-pathway rate and the action-selection model predict strong (positive or negative) correlations between pallidal neurons. However, all correlations studies (e.g. Raz et al., 2000; Bar-Gad et al., 2003a) of pallidal neurons in the normal monkey revealed lack of correlation between the spiking activity of these neurons.

The complex anatomy of the basal ganglia and the physiological correlation studies point to a different neural network approach to information processing in the basal ganglia. One example is the *Reinforcement Driven Dimensionality Reduction (RDDR)* model (Bar-Gad et al., 2003b). The RDDR model postulates that the basal ganglia can be modeled as an actor/critic reinforcement learning neuronal network whereas the goal of the system is to maximize the (discount) expectation of all future reinforcements by dynamic modification of behavior. The reinforcement signal is provided by the midbrain dopaminergic (the critic) projections to the striatum, i.e., to the actor networks of the basal ganglia. The dopamine-reinforcement signal represents the mismatch between expectations and reality or the temporal difference (TD) error. In the normal primate the background dopamine activity (5–10 spikes/s) represents a match between the animal's prediction and reality, whereas elevation or suppression of dopaminergic activity represents a situation where reality is better or worse than predictions, respectively (Morris et al., 2004). The actor part of the basal ganglia network (cortex; striatum and STN; GPe and GPi) compress cortical information using reinforcement controlled cellular (Hebbian and anti-Hebbian) learning rules. The ultimate goal of basal ganglia actor is to achieve optimal behavior or policy, e.g., optimal state-action (stimulus-response) associations, by modification of the efficacies of the gigantic matrix of $>10^{13}$ cortico-striatal synapses. This setting of the cortico-striatal functional efficacy leads to optimal connectivity between the sensory and the frontal cortices and optimal behavior which maximize expected future reward. Optimal representation of the state-action matrix in the actor part of the basal ganglia networks is achieved by decorrelation of the spiking activity of the pallidal neurons (output stage of the basal ganglia). The model suggests that the chronic dopamine depletion in the striatum of PD patients is perceived as encoding a continuous state whereas reality is worse than predictions. This lead to modifications in the delicate high-dimensional matrix of efficacies of the cortico-striatal synapses and abnormal synchronization of

the basal ganglia networks (in additions to changes in firing rate and pattern). Furthermore, inappropriate dopamine levels – as, for example during pulsatile dopamine replacement therapy – will cause abnormal random organization of the cortico-striatal network, and eventually would lead to dyskinesia (inappropriate state-action pairing).

Results: Synchronized activity in the basal ganglia

Multiple electrode studies analyzing for correlations of pallidal neurons in the normal monkey revealed lack of correlation between the spiking activity of these neurons (e.g. Raz et al., 2000; Bar-Gad et al., 2003a). These studies have shown an increase in both oscillatory activity and in neuronal correlation of pallidal cells in MPTP primates (Raz et al., 2000; Heimer et al., 2002). This increase in pallidal synchronization has been shown to decrease in response to dopamine replacement treatment (Heimer et al., 2002).

However recent human studies have found oscillatory neuronal correlation only in tremulous patients and raised the hypothesis that the increased neuronal synchronization in Parkinsonism is an epi-phenomenon of the tremor or of independent oscillators with similar frequency (Levy et al., 2000). Human studies are limited by constraints related to recording duration, selected anatomical targets and clinical state of the patients (e.g., most surgical patients have undergone many years of dopamine replacement therapy (DRT) and have already developed dyskinesia). We therefore investigated the role of oscillatory activity and of neuronal correlation throughout the different clinical states of PD in the MPTP primate models of this disease. The tremulous vervet monkey and the rigid-akinetic rhesus monkey were selected to imitate tremulous and non-tremulous subtypes of human patients. We combined multi-electrode recordings with a newly improved tool for spectral analysis of both single cells discharge and interneuron relations (Rivlin et al., 2006) and distinguished between neuronal correlations of oscillatory nature and non-oscillatory correlations. We found that a major fraction of the primate pallidal cells develop both oscillatory and non-oscillatory pair-wise synchronization, following the induction of dopamine depletion and PD clinical signs. Non-oscillatory burst oscillations were mainly found in the GPe, whereas 10 Hz synchronous oscillations were dominant in the GPi. In contrast with the study of human patients, we found oscillatory activity in both the tremulous and the non-tremulous monkey. Clearly, non-oscillatory synchronized burst cannot be the result of a common tremor drive or of independent oscillators with similar frequencies. Moreover, our theoretical analysis of coherence functions revealed that small changes – such as of 0.1% of the basic oscillatory frequency – between the oscillation frequencies of two simulated neurons would result in non-significant coherence value if the recording duration is equal or longer than 10 minutes. Therefore, we can rule out the possibility of false detection of significant coherence in the typical recording duration applied in our primate recordings.

Discussion

The basal ganglia networks can be modeled as an actor/critic reinforcement learning network. The actor networks connect all cortical areas through the basal ganglia with the executive areas of the frontal cortex. The midbrain dopaminergic neurons (the critic) provide a temporal-difference error message to the striatum controlling the efficacies of the cortico-striatal synapses. The distribution of the cortico-striatal efficacies represent the state-action matrix (policy) implanted by basal ganglia. Under normal dopamine influence, the basal ganglia provide an optimal representation of state-action matrix, resulting in non-correlated activity of neurons in

the output structures of the basal ganglia. However, in dopamine depleted subjects the striatum faces an unremitting message of ''reality worse than predictions'' leading to modification of the efficacies of the cortico-striatal synapses and abnormal synchronization of basal ganglia activity. Current DBS methods overcome this probably by imposing a null spatio-temporal firing in the basal ganglia enabling the thalamo-cortical circuits to ignore and compensate for the missing basal ganglia. We therefore suggest that future DBS methods should be directed towards manipulation of the abnormal synchronization of the basal ganglia in PD. This may be achieved by multiple micro-contacts within the DBS targets, rather than the single macro-contact used today.

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Basal ganglia discharge abnormalities in Parkinson's disease

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Summary. In the traditional model of the pathophysiology of parkinsonism, parkinsonian motor signs are viewed as the result of changes in discharge rates in the basal ganglia. However, not all experimental findings can be explained by rate changes alone, and changes in discharge patterns in these nuclei are increasingly emphasized as pathophysiologically important, including changes in burst discharges, in synchrony, and in oscillatory activity. This brief review highlights the pathophysiologic relevance of these rate and pattern changes in the pathophysiology of parkinsonism.

Introduction

In early Parkinson's disease selective degeneration of a small number of dopaminergic cells in the lateral portion of the substantia nigra pars compacta (SNc) leads to the signs of parkinsonism. Both the behavioral specificity and the seemingly disproportionate magnitude of the effect of such a small lesion in the midbrain are artifacts of the anatomy of the basal ganglia. The functional specificity arises from the fact that the basal ganglia are topographically organized, and that the early degenerative process in Parkinson's disease affects predominately those SNc neurons that project to the motor portion of the striatum (the putamen) with relative sparing of other striatal areas. The magnitude of the behavioral effect of SNc lesions is explained by the fact that the basal ganglia are major components of circuits involving specific regions of the cerebral cortex and thalamus (Alexander et al., 1986) so that loss of dopamine in the motor portion of the striatum (the putamen) exerts strong effects on all other elements of the 'motor' circuit, including motor areas of the extrastriatal basal ganglia, and movement-related areas in thalamus and precentral motor fields. Thus, although pathologically a localized problem (at least initially), Parkinson's disease is pathophysiologically a disorder engaging the entire motor circuit. We here review the changes in neuronal activity that occur in this circuit in Parkinson's disease.

Changes in discharge rate

Inputs from cortical sensory-motor areas reach the basal ganglia through the putamen and the subthalamic nucleus (STN), while motor portions of the internal pallidal segment (GPi) and the substantia nigra pars reticulata (SNr) serve as output stations of the basal ganglia, projecting to the ventral anterior and ventrolateral nuclei of the thalamus. Information is conveyed between putamen and GPi/SNr through a monosynaptic GABAergic projection ('direct' pathway), and a polysynaptic ('indirect') pathway which involves the external pallidal segment (GPe) and STN.

Tonic GABAergic output from neurons in GPi/SNr is thought to inhibit their projection targets in thalamus, thereby reducing cortical activation. Dopamine, released from terminals of the nigrostriatal projection, is thought to facilitate transmission along the direct pathway, and to reduce transmission along the indirect pathway. These dual dopamine actions lead to a net reduction of inhibitory basal ganglia output, which may facilitate cortical activity, and eventually movement (Wichmann and DeLong, 2003).

Traditional models of the pathophysiology of parkinsonism are strongly influenced by this anatomic arrangement (reviewed in Wichmann and DeLong, 2003; Albin et al., 1989), which suggests that the overall amount of movement is in some way inversely related to the magnitude of basal ganglia output. According to the scheme mentioned above, loss of striatal dopamine within the motor circuit would result in increased STN activity, and increased basal ganglia output, reduced thalamocortical activity and the development of parkinsonian motor signs, such as akinesia or bradykinesia. Conversely, dopamine-induced dyskinesias have been postulated to result from decreased basal ganglia output.

The prediction that the discharge rates of neurons in the basal ganglia output nuclei and in the STN are increased in Parkinson's disease has been generally confirmed in animal models of Parkinson's disease, and is also supported by recording studies in humans undergoing functional neurosurgery as treatment for Parkinson's disease. Moreover, decreases in discharge in GPi have been found in animals with dyskinesias induced by administration of dopaminergic drugs.

It is noteworthy, however, that the predicted rate changes have not been found in all studies of parkinsonian subjects. More importantly, in a recent monkey study designed to test the rate-based model, we showed that increased STN and GPi rates (in this case produced by ibotenic acid lesions of GPe) are not *per se* responsible for parkinsonian signs (Soares et al., 2004). Despite rate changes similar to those in parkinsonian animals, the GPe-lesioned animals showed only minor motor impairments. Lesion studies have also demonstrated problems with rate-based models of parkinsonian pathophysiology. For example, based on the model, pallidal lesions would be expected to result in involuntary movements, but, in fact, have little effect on normal motor behavior. Similarly, thalamic inactivation, although predicted to induce parkinsonism, does not.

Pattern changes

Given that changes in discharge rate of basal ganglia neurons cannot fully explain the generation of parkinsonism or the production of drug-induced dyskinesias, changes in the activity patterns of basal ganglia neurons have been intensely studied. Although we will discuss here different types of pattern changes separately, all of them tend to occur in parallel, and may result from the same underlying mechanism(s).

Burst discharges

One of the firing properties that has been studied in detail is the incidence of burst discharges. Such burst discharges are a normal feature of basal ganglia discharge, and the timing and 'strength' of bursting may represent aspects of external events or behavior, probably representing the increased synchronization of cortical inputs to the subthalamic nucleus or striatum (Magill et al., 2000). In parkinsonism, the incidence of bursts is increased (e.g., Soares et al., 2004), most often in the context of synchronized oscillatory activity (see below). In part, this may occur because of an enhanced interaction between cortical areas and basal ganglia areas, particularly the STN, but other pathologic phenomena may also play a role. For instance, in dopamine-free co-cultures of STN and GPe cells, synchronized bursting

develops because of network properties (Plenz and Kitai, 1999). Prominent bursts in STN discharge have been shown to occur as rebound phenomena in response to prolonged or synchronized inhibitory GPe inputs to the STN (e.g., Bevan et al., 2002). Although less well studied, rebound bursts are also known to occur in other basal ganglia areas. Changes in inhibitory inputs to these areas may increase rebound bursting.

Synchrony

A second important phenomenon affecting the firing properties of basal ganglia cells in parkinsonism are changes in the synchrony of firing between neighboring neurons. Under physiologic conditions, the firing of neighboring basal ganglia neurons is largely uncorrelated (Bergman et al., 1994; Wilson et al., 2004). In the dopamine-depleted state, however, increased synchrony is observed in the STN (Bergman et al., 1994; Levy et al., 2002), in the pallidum (e.g., Heimer et al., 2002), in the striatum (between tonically active neurons, most likely corresponding to cholinergic interneurons) (Raz et al., 2001), and in frontal cortical areas (Goldberg et al., 2002). The link between synchrony and dopamine depletion is most clearly revealed by the fact that treatment with dopaminergic agents rapidly reduces the interneuronal synchronization observed in parkinsonism in the monkey pallidum (Heimer et al., 2002) and in the human STN (Levy et al., 2002). However, the mechanisms by which dopamine exerts these effects remain unclear. It has been proposed that dopamine loss in the striatum may trigger enhanced electrotonic coupling between neighboring striatal cells (see, e.g., Onn and Grace, 2000), or activity changes in interneurons or axon collaterals (Guzman et al., 2003). In the STN, synchrony is more likely to be the result of synchronous (or divergent) inputs from external sources rather than locally generated (Wilson et al., 2004). The potential synchronizing effects of local dopamine loss in GPe, GPi, or SNr, has not been explored in detail.

Oscillations

A third major change in the discharge patterns of basal ganglia neurons in parkinsonism is that dopamine loss enhances the tendency of neurons in the basal ganglia-thalamocortical circuitry to discharge in an oscillatory pattern (Soares et al., 2004; Bergman et al., 1994). These oscillatory changes are rapidly reversed by systemic treatment with dopaminergic agents (Levy et al., 2002), and are therefore likely to represent a direct effect of dopamine deficiency. Such oscillations are mostly confined to the extrastriatal basal ganglia, and characteristically occur in the alpha- and beta frequency bands. For instance, in parkinsonian monkeys and patients, oscillatory bursting typically emerges in both the 3–8 Hz band, and a power spectral band around 10 Hz (Bergman et al., 1994; Levy et al., 2000). Local field potential (LFP) recordings through implanted deep brain stimulation (DBS) electrodes in GPi and STN of untreated parkinsonian patients have shown similar oscillatory activity in the 10–30 Hz range, likely reflecting synchronized oscillatory neuronal spiking (Levy et al., 2002; Brown, 2003). Given the relation between the basal ganglia, thalamus and cortex, it is not surprising that pathologic oscillatory activity in the 'antikinetic' 10–30 Hz band has also been observed in areas of cortex that are related to the basal ganglia in parkinsonian patients and animals (Goldberg et al., 2002). MEG studies have also identified an oscillatory network with pathologic coupling at 10 Hz in patients with parkinsonian tremor, which included multiple cortical motor areas, as well as diencephalic and cerebellar areas (Timmermann et al., 2003).

Global engagement of the basal ganglia-thalamocortical circuits in synchronized oscillatory bursts may severely disrupt processing