Trevor W. Robbins

Born:

London, U.K.
November 26, 1949

Education:

Jesus College, University of Cambridge, B.A., 1st Class Honors, (1971)
Jesus College, University of Cambridge, PhD (1975)

Appointments:

University Demonstrator in Experimental Psychology, University of Cambridge (1973–1978)
University Lecturer in Experimental Psychology, University of Cambridge (1978–1992)
Reader in Cognitive Neuroscience, University of Cambridge (1992–1997)
Professor of Cognitive Neuroscience, University of Cambridge (1997–present)
Professor of Experimental Psychology and Head of Department of Psychology, University of Cambridge (2002–present)

Honors and Awards:

Spearman Medal of the British Psychological Society for Outstanding Research, 1981
Fellow of the British Psychological Society, 1990
Fellow, Downing College, Cambridge, 1990
DM Marquis Prize of the American Psychological Association for Best Paper in *Behavioral Neuroscience*, 1997
Chair, Neuroscience and Mental Health Board of the Medical Research Council, 1996–1999
President of the European Behavioural Pharmacology Society (EBPS), 1992–1994
President of the British Association for Psychopharmacology, 1996–1998
Fellow, Academy of Medical Sciences, 1999
ISI Most-Cited Neuroscientists List, 2001
Distinguished Achievement Award EBPS, 2002
IPSEN Foundation Prize for Neuronal Plasticity, 2005
Fellow, Royal Society, 2005
Fred Kavli Distinguished International Lecturer Society for Neuroscience, 2005
President, British Neuroscience Association, 2009–2011
Distinguished Scientific Contribution, American Psychological Association, 2011
European Brain and Behaviour Society, Behavioural Brain Research Award, FENS, 2012
Angharad Dodds John Fellow in Mental Health and Neuropsychiatry, 2012
Commander of the British Empire (CBE), 2012
Grete Lundbeck European Brain Research Foundation: Brain Prize, 2014
Lifetime Achievement Award, British Association for Psychopharmacology, 2015

Trevor Robbins has striven to synthesize cognitive and behavioral neuroscience with neuropsychopharmacology. He has defined cognitive and behavioral functions of cortico-striatal and limbic-striatal systems, as well as their chemical neuromodulation by the monoamines (dopamine, noradrenaline and serotonin) and acetylcholine. He has achieved bidirectional cross-species translation of findings from experimental animals to patients using the CANTAB computerized neuropsychological battery, which he co-invented. has pursued possible pharmacological treatments in patients with neuropsychiatric and neurodegenerative disorders ranging from ADHD and schizophrenia to Alzheimer's and Parkinson's diseases. He is responsible, with BJ Everitt, for a theory of drug addiction that proposes that transitions from goal-directed to habitual responding underlie compulsive drug-seeking and taking behavior and that these transitions are paralleled by a devolution of control from the ventral to the dorsal striatum, as well as a loss of "top-down" control from the prefrontal cortex.

Trevor W. Robbins

Early Life and Education: From Dopamine in South London to Inner Space at Cambridge

I was born in south London in 1949, first child of parents William and Eileen in a conventional family later to include my younger sister, Rita. Neither parent was able to attend University; both had had to leave school early because of World War II, which devastated London and left an aura of austerity over my early years. Among my first memories are watching the English cricket team winning the Ashes against Australia on a grainy black-and-white television at my grandparents' house, while mother was at work. From about four years of age, we lived close to one of those oasis-like green parks that provide sanctuary from the urban reality of south London. Bizarrely, I was to discover in later life a remarkable coincidence associated with this space, which I used throughout childhood as a playground that presumably enhanced my synaptic plasticity. The Georgian house that dominated the park and served as an elegant café for Sunday revelers had a scientific history. Dopamine was first synthesized there. I later read in an article by Hornykiewicz (1986), who had inspirationally applied neuroscientific discoveries by Carlsson and others to test effects of L-Dopa in Parkinson's patients, that dopamine had been synthesized in south London, and naturally I wanted to know exactly where. A piece of Web-based research, leaning on biographies of Fellows of the Royal Society gave me the answer. Burroughs-Wellcome had used the Georgian House in Brockwell Park as a physiological research laboratory, under the leadership of no less a figure as Sir Henry Dale, famous for his early research into neurotransmitters and the dictum (now since disproven) that each neuron has but one transmitter. One of his research assistants, Arthur Ewins, had synthesized dopamine, which then was known by its chemical name of 3-methoxytyramine, publishing a paper with Barger in the *Journal of the Chemical Society* in 1910. The chemical initially was concluded to be a weak sympathomimetic substance of no obvious significance (Barger and Dale 1910). It was later to gain in importance, and especially for my own career.

Another neuroscientific coincidence illuminated my early life, as I played with my cousins in an apartment close to Holborn in central London. My aged aunt in her 80s reminisced with me about those times and when I asked where the apartment was she said it was in Queens' Square, "opposite the famous hospital." The famous hospital was in fact the National Hospital, the leading center for neurology in the United Kingdom, where all of the

famous British neurologists (and many others from overseas) trained and practiced (and where I later took a period of sabbatical leave in the 1980s to gain experience in clinical neuropsychology). In fact, the apartment in which they lived across the Square was Alexandra House, now home of the Institute of Cognitive Neuroscience of University College London, another later source of intellectual stimulation from neuropsychologists such as Tim Shallice.

I was academically good at school and managed to pass the dreaded 11-plus (at age 11) examination by which children were streamed into those attending grammar schools and those attending secondary modern (high) schools. Rather than aiming high and seeking a scholarship at the élite Dulwich College (a significant public, i.e., fee-paying, school), I decided to sample state education at Battersea Grammar School, situated in the suburb of Streatham, south London, which turned out to be an excellent choice. I tried my hand at everything, including drama, sports, and also chess, as the school was blessed with a number of young chess prodigies. I later led our school team to win the prestigious Sunday Times British Schools Chess Championship, won the London Junior Championship (under 14s), was ranked in the top 20 players in the country and even represented England Juniors at Board 1 before winning a succession of "half-blues" for representing Cambridge versus Oxford in varsity matches. Becoming strong at chess was a definite influence on my later interest in cognitive psychology and later became a focus of an interesting diversionary study into chess and working memory with the distinguished cognitive psychologist Alan Baddeley (Robbins et al. 1995).

On the academic side, I was good at both sciences and the humanities, eventually opting for the former—as the trend then and now in U.K. education was specialization and focus, rather than the liberal arts of the United States or the Baccalaureate-style European education. You were expected to maintain intellectual breadth by your vocational activities rather than through formal training. (I have endeavored ever since to maintain those vital interests in literature, drama, music, and visual arts in this way). The school generally had at most one or two pupils going to Oxbridge every year, and I used these role models to shape my future career goals. I plumped eventually for biology as my main interest, followed by chemistry. I had been inspired by reading in the *London Evening Standard* an article about the genetic code—probably about the time that the codons were identified. I understood that much of the work was being done in Cambridge, beginning of course with Crick and Watson, and immediately set my sights on biochemistry and molecular biology and Cambridge—to understand how living things actually worked.

To apply to Cambridge in those days, you had to have two languages, other than English. I had kept up with French, but had to give up classics, being in the science stream. So I had to study Latin in my spare time to

pass the exam necessary for qualification for Cambridge. (I passed, although just before the exam they waived this requirement.) I took the Cambridge entrance exam in the last year at school, which was a little early; (most candidates take an extra year). To my astonishment, I was offered an interview at Jesus College (I had no idea which college I should apply to and just took after the example of my history teacher). Fortunately, after recovering from an early trap of my own making in the interview, I was offered a place to read the Natural Sciences Tripos (NST).

The NST was a flexible course, and I homed in on biological options. To be honest, I was slightly disappointed with the course material, which seemed to go over old ground that I already had covered at school (but probably did not really understand as well as I had thought). The second year offered an intriguing option of experimental psychology, which I took with biochemistry and zoology and instead of physiology, to make up my three offerings. The supervision or small-group tutorial system at Cambridge (whereby students are taught generally in twos or threes and write essays or do work for discussion) already had exposed me to some superb teachers in biology, but I met up with a lasting influence at this stage—Dr. Susan Iversen. Susan Iversen combines charisma with high intelligence in every domain, including the all-important social one; she is a truly inspirational and warm person. Susan Iversen actually had read zoology but had assimilated large parts of experimental psychology, which she taught with élan and enthusiasm. The result was that I was attracted to specialize (major) in psychology in my final year, and I did a research project with her on the effects of d-amphetamine on exploration in rats. I realized about this time that Susan Iversen was married to another important influence, Leslie Iversen, a master neurochemist who had remarkably assumed directorship of the Medical Research Council (MRC) at Cambridge at an early age and who had lectured with some gentle skepticism on his part on the molecular basis of memory and learning.

The final undergraduate year went quickly and I was enraptured by psychology, especially as it related to the brain—Susan Iversen's course was quite important. I also enjoyed the discipline of animal learning and the brilliant Michael (later Professor) Morgan's maverick approach. I was fortunate to attend the late Donald Broadbent's guest lecture series, which revolved around chapters of his yet-unpublished masterwork on *Decision and Stress* (1971), which has remained another major influence in several ways (although it has been surprisingly undervalued by experimental psychologists). The head of department was Oliver Zangwill, one of the fathers of British neuropsychology, and one of the main forces that had introduced the likes of Larry Weiskrantz and nonhuman primate work to Cambridge (and the United Kingdom). Zangwill was to play an important part in one of my personally momentous decisions—not to become a clinical psychologist. I had obtained a place on the prestigious master's course in clinical

psychology at the Institute of Psychiatry in south London, close to my birthplace at Dulwich Hospital. My mother had suffered from panic attacks and agoraphobia and had been well treated at this renowned center, and in a sense, that experience had motivated my interest in psychopathology. I was also more generally interested in motivation, that is, what made people tick. I was fortunate enough to get a first class result in the final exam, and this led Zangwill to ask, in his inimitably understated way, whether I would like to take up a place to read for a PhD at Cambridge, with Susan Iversen. Earlier, I had considered doing a PhD and had traveled to the University of Sussex to meet the redoubtable Professor Stuart Sutherland who was building an outstanding department in experimental psychology, especially learning. Decisions, decisions—one of the few real decisions you have to make throughout life—I plumped for research in Cambridge with Susan Iversen, although I did not really have a good idea of exactly what was entailed.

Graduate Life at Cambridge and Denmark: Early Studies on Psychomotor Stimulant Drugs

Thus ensued an ultimately happy but somewhat chaotic time. There were no taught courses in those days and you essentially had to pick up research techniques as opportunities arose, and also had to adopt a thematic approach to research that ultimately would generate a PhD thesis within three years. I was in laboratory with several of Susan Iversen's other research students. Particularly helpful and a constant source of inspiration and enthusiastic motivation was Ian Creese who later worked with Solomon Snyder to discover the dopamine receptor. Arjun Sahgal was completing a major thesis on memory systems in rhesus monkeys and baboons and later became a prominent U.K. neuropsychologist and psychopharmacologist. My early predoctoral period at Susan Iversen's direction was rather like a modern lab rotation doctoral course—I also spent time in Leslie Iversen's laboratory investigating the biochemistry of amphetamine metabolites and found I was just about competent to perform such studies but this was not likely to be my main strength (and I'm sure that Leslie Iversen would have agreed.). I also had a clinical project with Susan Iversen working with the neurologists in Cambridge on Parkinson's disease. We used a sophisticated way of measuring motor function in these patients based on Fitt's Law to quantify the possible benefits of a drug called amantadine. I learned an important lesson that for all the sophistication, I could not detect when amantadine was added to the usual L-Dopa theory or not. One of the patients found that he couldn't actually get up from bed upon amantadine withdrawal, however; that was a big effect, but it appeared in only one of the patients studied, which provided another early lesson in terms of clinical heterogeneity. Susan Iversen was a tremendous mentor and her and Leslie Iversen's extensive U.S. contacts arising from their time at NIH and Harvard Medical

School meant that a constant succession of luminary neuroscientists visited them at home where Susan Iversen's enormous networking skills came to the fore in a most exciting and fortunate manner for a graduate student. I remember meeting people like Julius Axelrod, Brenda Milner, Mortimer Mishkin, Karl Pribram, and Snyder all from their visits to Cambridge over lunch at the Queens' Head pub or chez the Iversen soirées. Particularly thrilling was a personal communication Leslie Iversen relayed to us via Susan Iversen that "Sol has discovered the opiate receptor."

My thesis went quite well; I expanded my undergraduate project to publish my first paper in the journal *Psychopharmacologia* (Robbins and Iversen 1973a). That first paper is always a little mysterious and exciting. I was focused on ways of affecting the central dopamine systems, beginning with the (rather dirty) method of simply investigating effects of systemic injections of amphetamine and dopamine agonist drugs in rats. I had the idea from the Broadbent book of using signal detection theory to characterize effects of the drug on performance, before I realized that David Warburton at Reading University already had had the same idea and had published on the method with cholinergic drugs. Nevertheless, I was able to publish a paper with Susan Iversen in a new journal from the *Nature* stable, *Nature New Biology*, which applied the method (Robbins and Iversen 1973b).

One of my first experiments from that period was never published except for being mentioned in chapters. I had looked at the effects of high doses of amphetamine and was especially interested in the cascade of behavioral changes that occurred to culminate in a bizarre syndrome of repetitive behavior, called stereotypy. I was fascinated that this occurred in all vertebrate animal species studied from human stimulant addicts to the lamprey and that it provided a potential model of psychopathology, relevant perhaps to psychosis (Randrup and Munkvad 1967). My experiment investigated how learning interacted with stereotypy. What I found was that in rats trained to work under a fixed ratio schedule of lever pressing to collect water from a dipper, this behavior often was suppressed. There would be, however, periods in which the learned behavior itself became stereotyped and repetitive—that is, the rats would continue to approach the empty dipper or, even more dramatically, they would continue to press the lever without bothering to collect the earned water reinforcement. The behavior was clearly abnormal, but rather than being random and arbitrary, it was based on the animal's previous experience and training. Later studies showed similar effects of the dopamine agonist apomorphine (see Figure 1). This seemed to be a remarkable model of psychopathology—what appeared to be grossly abnormal behavior with little apparent purpose, dependent on the drug effect (presumably on striatal dopamine) interacting with the animal's past history. (I later investigated with Guy Mittleman possible coping, stress-reducing response properties of stereotypy, although somewhat inconclusively).

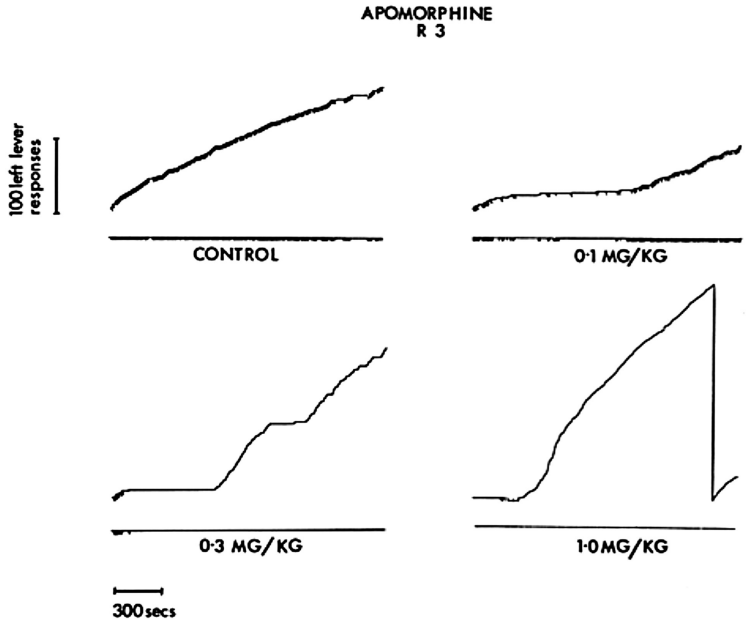

Fig. 1. The effects of the dopamine direct agonist apomorphine to produce stereotyped operant behavior. Rats are trained to respond across two levers, which unpredictably produce food reward. The normal pattern of responding on the levers is shown by the increments in cumulative pen record, with responses on the left lever incrementing on the y-axis and responses on the right lever causing downward ticks. Visits to the food magazine to collect earned food pellets are shown in the bottom record. Apomorphine treatment results in a focusing of responding onto one (the left lever) and a reduction in food magazine responses; the result is stereotyped lever pressing with no apparent purpose. This behavior is occurring at doses that normally cause typical oral stereotypy by this drug but evidently can be extended to incorporate previously learned responses (Robbins and Watson, unpublished data circa 1979).

This stereotyped instrumental behavior, although never published in full, and a persistent challenge for explanation throughout my career, led me to what I initially thought was an intriguing idea that behavior could be supported just by stimuli that previously had been associated with reward, that is, conditioned reinforcers, and I found that an industrial behavioral pharmacologist called Ronald Hill had had a similar idea, which he had published in an *Amphetamine Symposium* volume (Hill 1970). I developed the idea in my thesis using what I had learned from animal learning theory, and although the results were good enough for a thesis, I never did quite nail this idea to my satisfaction until my postdoctoral period when I was able to publish a single-authored paper in *Nature* (Robbins 1976) on this topic.

One consequence of my research into stereotypy is that I became interested in a Danish laboratory led by Axel Randrup that had published those

intriguing cross-species studies alluded to earlier and that was embedded in what I came to learn was one of the largest mental hospitals in Europe. The ready availability of short travel grants from the European Training Program enabled me to spend six months at this center in the town of Roskilde some 20 miles from Copenhagen, Denmark. I stayed in a guest room in a research laboratory and thus had first-hand experience of in-patients sometimes hallucinating as they wandered through the hospital grounds. In addition to Randrup, who was a positive, original thinker with some mildly eccentric qualities, the laboratory housed talented neuropharmacologists who were to become influential to the field: Claus Braestrup, who later participated in the discovery of the benzodiazepine receptor; Mogens Nielsen; and Jorgen Scheel-Kruger, who completed some important early studies on the different neuronal mechanisms by which amphetamine and methylphenidate produced their effects.

I also met Melvin Lyon, an American behavioral neuroscientist who had settled there and quickly began to work with him in designing some operant studies, as I had been intrigued by his similar findings of learned influences on stereotyped behavior produced by amphetamine in dramatic studies of avoidance learning (Lyon and Randrup 1972). In fact, although these started in a promising way, the laboratory was hit by a rodent infection halfway through the studies, and I therefore had the frustration of not being able to do much laboratory work for a portion of my visit. This setback, however, did give me the opportunity to spend much time in intense and friendly discussion with Lyon, which led to a major review we undertook of the behavioral studies of effects of stimulant drugs. We came up with the generalization that such drugs (and by implication striatal dopamine activation) produced "an increasing rate of responding in a reducing number of response categories." I was encouraged in this theorizing by the dramatic and pioneering account by O. Sacks in his book *Awakenings* (1973) of effects of L-Dopa in Parkinson's patients (e.g., especially Rolando P.) who had developed the disease through the encephalitis lethargica epidemic. We found a home for the somewhat lengthy article in a new book series of reviews (Lyon and Robbins 1975). I was grateful for this future fodder for my PhD thesis and also for future citations to the Lyon and Robbins synthesis by the likes of one of my heroes, Urban Ungerstedt. Ungerstedt had crowned the efforts of the seminal work completed by the Karolinska group on the neurobiology of dopamine systems in a now-legendary series of studies using the selective neurotoxin 6-hydroxydopamine (6-OHDA; e.g., Ungerstedt 1971). A highlight of my trip was the visit he hosted for me to the Karolinska Institute in Stockholm. Another, at the end of my stay, was a trip to Rotterdam to attend my first international meeting of the European Brain and Behaviour Society (EBBS), where I gave my first oral presentation; Edmund Rolls, then at Oxford, was a helpful mentor during this mildly stressful episode.

I had two enormous life-changing events on my return to Cambridge. First, amazingly, I was appointed to the faculty of the Department of Experimental Psychology as a Demonstrator—a sort of junior lecturer post specializing in practical teaching (I helped, sometimes counterproductively, in Zangwill's spell-binding hypnosis demonstrations). This was a kind of five-year research plus teaching fellowship, which no longer exists in Cambridge, but which invaluably gave young scientists the opportunity to develop a career platform before generally moving on. Second, soon after my return, I met an amazingly clever and stunningly beautiful woman with the somewhat exotic name of Barbara Sahakian, Susan Iversen's first-ever U.S. graduate student who had come to Cambridge to work with the Iversens on the effects of postweaning social isolation in rats. These animals, which were essentially deprived of social play during adolescence, developed striking patterns of behavioral hyperactivity and stereotypy that resembled effects of amphetamine. Sahakian thought that the isolated rats' behavior potentially modeled the human attention deficit/hyperactivity disorder (ADHD) and was keen to show that the stimulant drug therapy may lead to stereotypy in these adolescents. Indeed, the rats showed dramatic increases in stereotyped responses to amphetamine that suggested changes in brain dopamine function caused by this early social experience (Sahakian et al. 1975). (Only later, when we had established a neurochemistry laboratory in the department, working with graduates Graham Jones and Scott Hall and postdoc Lawrence Wilkinson were we able to demonstrate this in fact to be the case; see Wilkinson et al. 1994). I became interested in Sahakian's project and indeed we became interested in one another in what would become a lifelong partnership and collaboration, which has culminated with us living together as full professors at Cambridge.

The next couple of years were of consolidation of personal and professional life. The PhD thesis was duly submitted (and accepted) with my feeling that it was really a sketch toward the studies I really wanted to do. I bought a house in Cambridge for £8,100 (about $12,000) on a salary of £2,500 per year (homes in Cambridge now cost nearly 60 times as much). The laboratory saw new graduate students such as Michael Petrides, later director of Cognitive Neuroscience at the Montreal Neurological Institute; Nicholas Tye, who shared our house and later worked with Eli Lilly and Company to produce the successful antipsychotic olanzapine; and Peter Kelly, a dynamic and enterprising postdoc of Susan Iversen's from Oxford who was soon to produce some compelling evidence using 6-OHDA that the locomotor hyperactivity produced by amphetamine was due to dopamine release from the nucleus accumbens within the ventral striatum (Kelly et al. 1975), whereas the behavioral stereotypy had already been shown by Creese and Iversen (1975) to be due to dopamine in the dorsal striatum (I having expertly observed and provided behavioral ratings for that study). Other influential colleagues included two bright graduate students of Susan Iversen's, Stephen

Mason and Paul Fray. Between them and Arjun Sahgal, they managed to help the lab develop new sophisticated methods for controlling experiments by computers, online partly through an inspirational link with new microprocessor-based technologies in collaboration with exciting new computer-based industry in Cambridge (Silicon Fen) through companies such as Acorn, led by the brilliant entrepreneur (and my friend) Hermann Hauser.

My major experimental thrust was to follow up the idea that stimulant drugs enhanced the effects of stimuli associated with reward, that is, conditioned reinforcers, an idea that much later became renamed incentive salience by Kent Berridge and Terry Robinson (1998) at the University of Michigan. The key paradigm, of several I tried, was first to associate an arbitrary conditioned stimulus with a reinforcer, such as food or water (or rewarding brain stimulation, or a drug) and then to determine whether rodents would learn new responses to obtain these conditioned reinforcing stimuli. Amphetamine-like drugs greatly potentiated the rate of responding on the novel lever providing the conditioned reinforcer. One unusual drug with which Hill had worked, called pipradrol, originally developed as a drug to enhance cognitive performance in the elderly, produced particularly strong and less (frustrating) individual variation of effects than d-amphetamine, and I used this for all my early studies of this striking phenomenon. Even then, I was struck by the pathological nature of this behavior—rats sometimes would respond thousands of times for these stimuli, which no longer signaled water reward, and they no longer bothered to visit the former location where the reinforcer water had been delivered. If required to learn a two-response operant chain (e.g., press left and then right) to turn on the conditioned reinforcer, they ended up increasing their response on the response closest to the former reward—thus not resulting in any feedback stimuli at all, except for whatever proprioceptive and kinaesthetic feedback they obtained from their own behavior. This seemed to me a profound model of psychopathology under what was presumably a high dopamine state. It reminded me not only of my earlier observations of stereotyped behavior in rats but also of accounts I had read in Bleuler's classic work *Dementia Praecox* (1950) of patients with schizophrenia, whose sometimes bizarre and apparently irrational behavior was driven by events and associations formed in their past. Bleuler had stated in his great work that stereotypy was in the thoughts and stereotypy was "in the thinking and in the desires of the hallucinating patients" desires of the hallucinating patients (1950, p. 185). These data and ideas were submitted to *Nature* in the single-authored paper referred to above which to my great surprise was accepted for publication (Robbins 1976) and almost certainly contributed to my 1978 appointment to a tenure-track lectureship at Cambridge and to my eventual long-time commitment to the place (although only after quite a few second thoughts).

I managed to sneak in a period of personal leave to visit the United States for the first time with Barbara Sahakian to meet her distinguished

parents in Boston, William and Mabel Sahakian, both professors of psychology and philosophy, as well as church ministers. In a mini-tour of the East Coast, during a visit to Johns Hopkins to see Creese and Snyder, we met up with another major influence, George F. Koob. Koob was to take up a postdoctoral visit to work with Susan and Leslie Iversen and wanted advice on how to live at Cambridge, England. He was to become an intellectual and practical mentor, initiating me into the rigors of stereotactic surgery, brain stimulation reward, and electrochemistry, while also becoming a lifetime friend and influential scientific colleague. We saw Koob in frequent visits and interchanges between Cambridge and San Diego, where he was to settle first at the Salk Institute, working with Floyd Bloom, and later at the Scripps Research Institute.

This period was followed a year or two later by a return, sabbatical stay in Boston, after Sahakian had completed her PhD, to work at Harvard Medical School with the "fathers of behavioral pharmacology," Peter Dews, Bill Morse, and Roger Kelleher—with whom Susan Iversen had earlier worked. I learned much in this brief stay, which was salutary for a humble psychologist—as this group was wedded to a brilliant but strictly no-nonsense behavioristic perspective inspired originally by B.F. Skinner and combined with equally no-nonsense classical pharmacology. The principles of rate (or baseline-dependency, Law of Initial Values) and the critical difference between concepts such as *reward* and *reinforcement* was soundly learned. I also was initiated into the then-influential behavioral pharmacology group in the United States being introduced to such luminaries as Joe Brady and Charles Schuster.

Functional Studies of the Central Monoamine Neurotransmitters in Cambridge, England

One practical lesson I learned from my studies of mice using Galen Wenger's apparatus at Harvard was that it might be feasible to train rodents in a multiresponse operant task in which they had to detect brief flashes of light presented randomly in space to earn food. I found that it was possible to use such an apparatus for rats and to quantify two somewhat-independent measures of performance, accuracy of detection, and premature responses as an index of response vigor (see Robbins 2002). This task was inspired by my readings from Broadbent's *Decision and Stress* (1971) of a set of studies done at the Cambridge Applied Psychology Unit on the "five-choice serial reaction time" for humans, directed at assessing the effects of such human factors as stress; extremes of noise, temperature, and incentives; and drugs, such as stimulants and barbiturates. Broadbent had theorized about the famous curvilinear (inverted-U-shaped function supposedly linking efficiency of performance to hypothetical levels of arousal in the central nervous system. His insight had been that you needed different inverted-U-shaped

functions to explain all of the effects of these stressors; they simply did not add up in a straightforward way. My later insight was that these different functions probably were mediated by the different chemical neurotransmitters affected by the various drugs—notably the monoamines, including dopamine, noradrenaline, and serotonin, and the substituted amine, acetylcholine (Robbins and Everitt 1995). Over my subsequent career, I developed the theoretical idea, including studies in humans as well as experimental animals, that different states (e.g., of mood or arousal) optimally favored particular fronto-executive functions, thus enabling a refined and sensitive tailoring of cognition that was most appropriate to the prevailing internal state or environmental conditions (see Robbins 2007).

The ambition to work on these ideas was greatly enhanced by my future scientific collaborations initially with Koob, and later with another Cambridge colleague, Barry Everitt, whom I had met at another EBBS meeting in Copenhagen 1976. It was a source of embarrassment to both of us in socializing with other delegates that we actually had not met in Cambridge, as we were working not more than 100 meters apart on different floors of the Departments of Experimental Psychology (myself) and Anatomy (Everitt). We resolved in the future to try working together on common interests, Everitt also having developed research on the monoamine systems from his own previous postdoctoral stay at the Karolinska Institute. This collaboration, one secret of which has been to retain our distinctive individual identities and contributions, has led to some inspired interactions. It has now lasted nearly 40 years, recently being marked by a joint award, specifically for the collaboration, from the American Psychological Association. The immediate products of the interaction were some of my first jointly funded grants with Everitt by the MRC to investigate the comparative roles initially of noradrenaline (reviewed in Everitt et al. 1990), and then (in the late 1980s and 1990s) acetylcholine and serotonin. This work eventually led to data showing quadruple dissociations of behavioral effects among these transmitters in their effects, for example, on the five-choice serial reaction time task described above, which were compatible with the type of theory concerning the differential functions of these transmitters (Robbins and Everitt 1995). I also gained some support from the Parkinson's Disease Society to investigate further the roles of dopamine using other behavioral paradigms, including one that postdoc Mirjana Carli and a smart graduate student John Evenden invented to examine the Ungerstedt-Marshall and Teitelbaum idea that unilateral striatal dopamine depletion led to *sensory neglect*. We refuted this hypothesis by suggesting instead that it was in reality a *response* or *intentional neglect* (Carli et al. 1985) that possibly was caused (from results of further studies; e.g., Brown and Robbins, 1989) by impairments in representing egocentric space.

We also explored which of the dopamine systems (i.e., the dorsal or ventral striatum) were responsible for the enhancement of conditioned

reinforcement. Early experiments using the 6-OHDA dopamine depletion techniques with Everitt suggested that it was the dorsal system, consistent with my theoretical view that it was a form of stereotypy. A brilliant and bold graduate student, Jane Taylor, confounded this view by showing with our first use of intracerebral infusions of drugs that the key area was the nucleus accumbens (Taylor and Robbins 1984). Moreover, further collaborations with a postdoc from Bordeaux, Martine Cador, and Everitt showed that the behavior was likely driven by the basolateral amygdala, which appeared to be responsible for encoding the conditioned stimulus-unconditioned reinforcer interaction (Cador et al. 1989). Together with other studies with Koob on food-associated incentive activity (Koob et al. 1978) and the exotic phenomenon of the acquisition of schedule-induced polydipsia (Robbins and Koob 1980), a form of compulsive drinking perhaps induced by overarousal, we began to hypothesize distinct roles of the ventral (i.e., nucleus accumbens) and dorsal (i.e., caudate-putamen) striatum for incentive motivation and stimulus-response coupling and execution, and under pathological circumstances, motor stereotypy (dorsal striatum; Robbins and Everitt 1992). I like to think that the former idea, which was consistent with views of the Tony Phillips–Chris Fibiger collaboration at the University of British Columbia (Fibiger and Phillips 1988), and owing something to Tim Crow's early provocative speculations (Crow 1973), presaged to some extent the seminal discoveries of Wolfram Schultz (1996) on the roles of midbrain dopamine neurons in reinforcement learning. These studies also stimulated Everitt and I to start thinking about how these systems might be implicated in drug addiction (see the following).

Translational Studies of Human and Animal Neuropsychology: The CANTAB

Another significant development for myself in the 1980s was my foray into work with nonhuman primates and humans. I have always had an interest in the translation of research into clinical utility, beginning with my early career aspirations in clinical psychology and fueled in the United Kingdom by an intense drive ethically to justify work with experimental animals by showing potential human benefit in relation to the costs to the animals themselves. The perfect opportunity to pursue this pipedream was made possible by a grant competition of the Wellcome Trust for a Major Award in relating neuroscience to mental health disorders. Stephen Dunnett had joined the Department of Experiential Psychology as a lecturer to investigate effects of neural transplants in experimental animals in Parkinson's, Huntington's, and (early) Alzheimer disease-type models, and this focused our attention on therapeutic strategies for ameliorating the profound cognitive deficits of these disorders. Most ambitiously, we also proposed to extend the analysis not only to the nonhuman primate (marmoset) model, but also to human

patients by using cognitive tests that could be generalized from animals to humans (a concept also popularized by Larry Weiskrantz at Oxford). We also borrowed another idea from Oxford researcher David Gaffan, to use touch-sensitive screens, to test not only monkeys (Gaffan's innovation) but also human patients. For a program that almost certainly now would be considered by many granting agencies as overambitious and lacking focus, we were amazed to be funded. This Wellcome Trust support, which has now lasted for some 30 years, has been instrumental in my development as a cognitive as well as behavioral neuroscientist, as it funded the development of what came to be called CANTAB (the Cambridge Neuropsychological Test Automated Battery; http://www.cambridgecognition.com/academic/cantabsuite/tests).

The CANTAB (Robbins et al. 1994, 1997) arose as a series of brainstorming discussions about new neuropsychological tests with members of the Wellcome Trust team we had brought together: Sahakian, Evenden, Angela Roberts, and Robin Morris. Sahakian, then a lecturer at the Institute of Psychiatry, London, led the piloting of these tests in patients with early Alzheimer's disease in one of the first memory clinics in the United Kingdom. We made sure that they could at least attempt the easiest forms of the tasks, which were based partly on tests that had been employed by Mishkin and others to map the neural systems implicated in visual recognition memory in rhesus monkeys. Other tests derived from the reverse perspective of decomposing a standard human neuropsychological instrument such as the Wisconsin Card Sorting Test (WCST), commonly used to test patients with frontal lobe damage, and presenting it in a form that could be learned by our chosen New World monkey, the marmoset. The WCST required subjects to learn a concept or rule on the basis of trial-and-error feedback from the clinical neuropsychologist before the rule was suddenly changed to require re-learning. Milner's famous (1963) finding had been that patients with frontal lobe damage, while learning the initial rule normally, perseverated in applying it when it was no longer correct. I had realized that the WCST was related to a paradigm that was then still influential in animal and human learning theory (Mackintosh 1983); the distinction between intradimensional (id) and extradimensional (ed) shift learning; the rule-shift in the WCST was equivalent to an analogous shift in which stimuli had to be attended in experiments with pigeons, rodents, and children. With Roberts working in our first studies in marmoset monkeys, we were able to show that marmosets apparently solved these rule-learning and shifting tasks in ways similar to those found in humans (Roberts et al. 1988). We later were able to exploit this similarity to test the precise neural substrates of attentional set-shifting in marmoset monkeys; one of the major aims of the CANTAB was to achieve this type of bidirectional translation from animal to clinical studies.

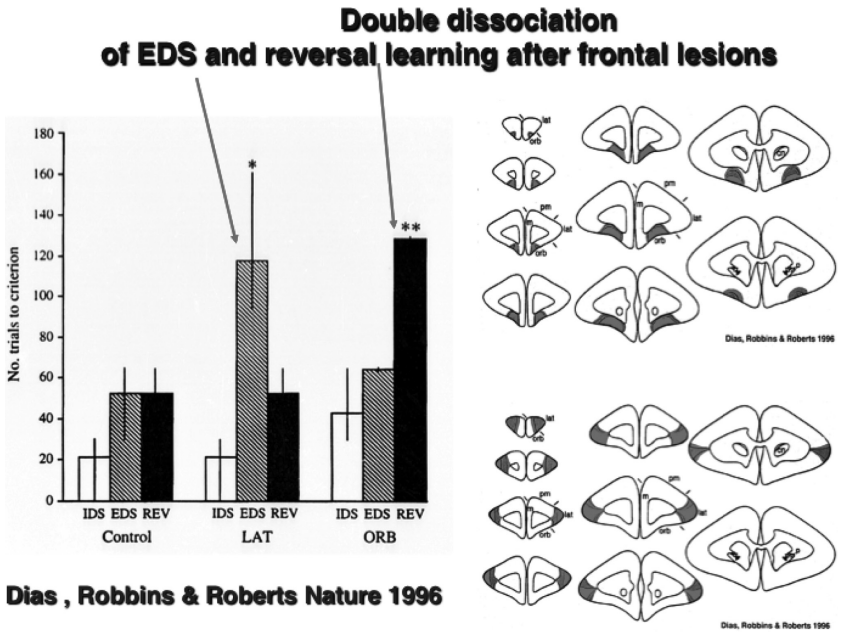

Fig. 2. Double dissociation of effects of lesions of the lateral prefrontal and orbitofrontal cortex in the marmoset on two forms of cognitive flexibility: extradimensional set-shifting and reversal learning. Reproduced with permission by *Nature Neuroscience* (Dias et al, 1996).

The CANTAB id/ed set-shifting task also incorporated yet another type of shift, in reversal learning. An id shift required the animal or human to continue to use a rule learned for one set of compound stimuli (i.e., stimuli varying in at least two dimensions) when confronted with a new set of discriminations. By contrast, for an ed shift, the subject had to shift to use the previously irrelevant cues to predict reward again when confronted with new stimuli over which to generalize the rule. For reversal learning however, the stimuli remained the same, but their significance for reward or punishment was shifted. Working with Rebecca Dias, Angela Roberts and I found that discrete lesions to different parts of the marmoset prefrontal cortex (PFC) produced doubly dissociable effects on ed shifting and reversal learning (Dias et al. 1996). Lateral PFC lesions produced ed shifting deficits but no effects on reversal learning, whereas orbitofrontal lesions produced deficits in reversal learning (as was already known) but no effects on ed shifting (see Figure 2). Thus, different circuits appeared to underpin these forms of cognitive flexibility and these findings have had a major effect on our thinking as well as an impact in several areas. Thus, for example, we also have used this paradigm to differentiate the roles of the catecholamine and serotonin neurotransmitters in the PFC for these different aspects of

cognition; the former affects id and ed shifting (see Robbins and Roberts 2007), whereas serotonin in the orbitofrontal cortex selectively influences reversal learning (Clarke et al. 2004). Moreover, former student Verity Brown and colleagues ingeniously turned the id/ed test for humans and monkeys into an assay for rodents but using different sensory modalities (smell and touch) rather than visual dimensions (Birrell and Brown 2000), which has been much used in the pharmaceutical industry. Another former graduate student, Timothy Bussey, has successfully developed a touch-screen behavioral test battery for rats and mice, based originally on work he initiated in the lab with discarded human touch-screens (Bussey et al. 1994, 2012). More generally, this work with marmosets stimulated an interest in defining the precise components of *fronto-executive* functioning.

A further example of a CANTAB test with pharmaceutical relevance was the five-choice serial reaction time task (5CSRTT). Originally adapted for rats from the classic human task, we back-translated it to humans, specifically patients with early Alzheimer's disease. The experimental program with Everitt on functions of the chemical transmitters had thrown up an interesting discovery about the functions of the cholinergic basal forebrain. Many investigators had been testing effects of destroying these neurons in the rodent brain to model more selectively the profound cortical cholinergic depletion that had been shown for patients with dementia. Although there were many reports of impaired learning and memory following such destruction, Everitt and I were skeptical that these impairments were entirely due to cholinergic loss because of the considerable ancillary damage caused to neural systems adjacent to the nucleus basalis magnocellularis (the likely homologue of the cholinergic nucleus basalis of Meynert in humans), such as the globus pallidus. This was particularly the case when the lesions were made with the nerve fiber-sparing excitotoxin ibotenic acid. For some reason, the cholinergic neurons themselves were apparently rather resistant to the effects of this neurotoxin in comparison with other cell groups. Experimentation and serendipity revealed that the cholinergic neurons were more susceptible to the excitotoxins quisqualic acid and later AMPA. The latter actually produced an apparent relative sparing of the noncholinergic cell groups, with a greater impact on cortical acetylcholine function and less evidence of significant behavioral deficits, at least in tests of memory and learning, such as the Morris water-maze and passive avoidance (Page et al. 1991). This was not true of performance on the 5CSRTT, in which robust attentional impairments were found that were reversible even by cholinergic agonists, such as the acetylcholinesterase physostigmine and nicotine and also remarkably by cholinergically enriched neural grafts obtained from rat embryos (Muir et al. 1992). The exciting parallel human study was being carried out by Sahakian and colleagues who were finding in one of the first ever trials of an anticholinesterase, tacrine, that the only objectively measured aspect of performance to show improvement following chronic treatment with the drug in patients

diagnosed with Alzheimer's disease was on the human CANTAB version of the 5CSRTT. The drug did successfully show small improvements on the standard clinical scales but not on objective measures of memory function. Thus, this translational rodent project successfully predicted the likely small, although significant, effects that cholinergic drugs can have on patients with dementia, that were mainly confined to enhancing alertness and attention, consistent with clinical findings (Sahakian et al. 1993).

I also learned several lessons from the animal part of this project; notably the importance of the necessity of specificity and selectivity of any manipulations designed to test the causal role of neural circuits in the brain—and in parallel, the importance of carefully assessing the consequences of such manipulations using appropriate histological and neurochemical assessments. Although we had achieved greater selectivity attacking the cholinergic neurons by varying the nature of the chemical neurotoxin we were using, presumably because of subtle differences in the molecular constitution of membranes of the cholinergic cell bodies, the achieved specificity was far from perfect. Indeed, a few years later, an even more selective immunotoxin (192-IgG saporin) was developed, and we were fortunately able to show that our basic findings held (Dalley et al. 2004). The constant refinement of techniques, however, means that further evolution of viewpoints is likely; the emergence of optogenetic and chemogenetic techniques, such as DREADDs, means that future hypotheses about the roles of the cholinergic system in attentional processing in the cortex are likely to be tested to the limit.

A second lesson was that converging evidence, where possible, using other techniques is also important to support working hypotheses. Thus, we were later able to show with Jeffrey Dalley using in vivo microdialysis, that acetylcholine is released during performance of the 5CSRTT in rats—and these findings have been further qualified by elegant work by Martin Sarter at Michigan using in vivo voltammetric techniques to quantify choline transients (Parikh et al. 2007). I recall that Martin and I first exchanged ideas about the functions of the nucleus basalis upon my consultancy visits to the Schering AG in Berlin, initiated by their scientific director and subsequent friend Dai Stephens, around the time of the falling of the Berlin Wall.

To strengthen my own experience in human neuropsychology I decided to take a period of sabbatical leave at the Institute of Neurology in London working with the eminent clinical neuropsychologist Professor Elizabeth Warrington, which I found to be an exciting and unique experience. My interest in Parkinson's disease, especially the suspected cognitive deficits in that disorder also led me into a crucial collaboration with the late Professor C. David Marsden and his group, which enabled me to test the utility of the CANTAB battery in an intense clinical setting. Marsden was then the leading expert on Parkinson's disease in the world and had strong views on the motor functions of the basal ganglia and whether Parkinson's disease patients had significant cognitive disorders. He generously allowed me

access to a tiny testing room situated just off his main office in the institute, and I was referred a large variety of clinical patients with all sorts of neurological impairments, ranging from idiopathic Parkinson's disease to a new malign syndrome called multiple system atrophy that resembled Parkinson's disease but was unresponsive to L-Dopa therapy and in fact etiologically was quite distinct. I was able to witness clinical phenomena such as bradyphrenia (slowed thinking) and even measure it using a CANTAB adaptation (the Stockings of Cambridge test) of Tim Shallice's Tower of London planning task that made it possible to measure the apparent speed of thinking. One patient I tested could solve almost all of the problems but only after a seemingly interminable period of reflection.

Using CANTAB, and with aid of a new talented and hard-working graduate assistant Adrian Owen, we were able to chart the course of Parkinson's disease from its earliest stages even before medication to its later stages during which it was clear that general cognitive intellectual deterioration was taking place (Owen et al. 1992). Owen also was testing patients with localized brain damage—for example, to the frontal or temporal lobes—to validate that the CANTAB tests indeed were probing the expected neural substrates and that our attentional set-shifting test was sensitive, like the WCST, to frontal damage in humans (Owen et al. 1990, 1991). The CANTAB tests (see some examples in Figure 3) especially probed what we decided to

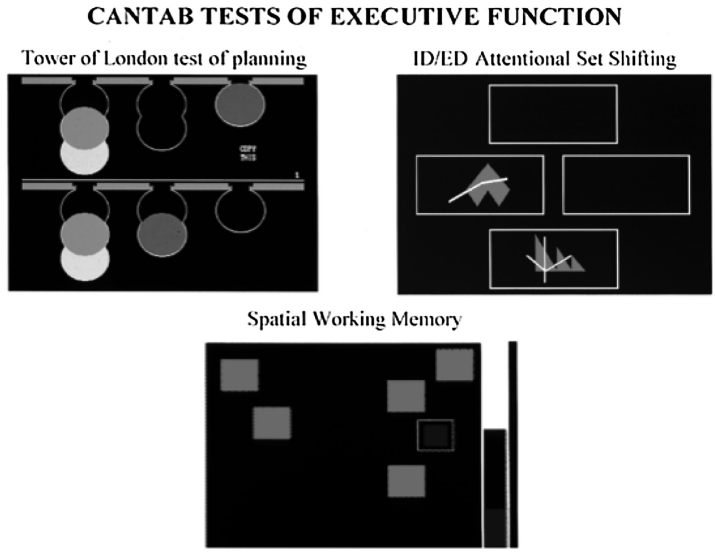

Fig. 3. Three CANTAB tests for three components of executive function: Tower of London planning task (also called the Stockings of Cambridge), the id/ed attentional set-shifting test, and spatial working memory. Reproduced with permission of *Cambridge Cognition, plc*.

be the most salient executive components, including cognitive flexibility, response inhibition, and working memory (Friedman et al. 2006; Robbins 2007; Robbins et al. 1998).

Of particular interest to me was whether L-Dopa medication prescribed for the motor impairments was of any additional use in treating cognitive impairments. We already had found that just-diagnosed, never-medicated patients did have significant problems with attentional set-shifting, suggesting to us that the nature of the cognitive impairments was reminiscent of a frontal disorder (we coined the notion of a "fronto-striatal" dementia) and demonstrating, at least for this function, that the drug could not be exerting significant deleterious effects. We tested the hypothesis that L-Dopa had significant effects on cognition in Parkinson's disease by testing patients on and off L-Dopa therapy, finding that performance on certain tests, planning as well as spatial working memory (using a human adaptation of the delayed alternation type tests in animals), was profoundly impaired by L-Dopa withdrawal, whereas performance on other tests (e.g., visual recognition memory) was not (Lange et al. 1992). The findings on spatial working memory were entirely consonant with Patricia Goldman-Rakic's seminal studies of the role of prefrontal dopamine in spatial working memory in monkeys, which had been a guiding inspiration for the CANTAB (Brozoski et al. 1979). These findings with Parkinson's disease patients were later to be complicated by several other intriguing results that reinforced a future lesson that, although informative and clinically useful, it is unwise to rely on findings obtained from studying a neurological disorder to study the functions of neural structures, such as the basal ganglia, or a chemical transmitter system, such as dopamine. Neurodegenerative diseases have far too many nonspecific and generalized effects to be effective "experiments of nature."

Firm evidence for these generalized effects came from studies much later in the 1990s by gifted graduate students Roshan Cools and Rachel Swainson, who both found essentially that whereas some aspects of cognition in Parkinson's disease, such as working memory, were improved by dopaminergic medications, other aspects were made worse (Swainson et al. 2000; Cools et al. 2001). We related these puzzling differences to differences in the degree of disease-related dopamine loss in parallel, functionally segregated fronto-striatal pathways of Alexander, DeLong, and Strick (1986), which hypothetically mediated different aspects of cognitive function. Thus, those pathways, predominantly in the dorsal striatum, that were most dopamine depleted exhibited the most therapeutically beneficial responses in terms to L-Dopa (most noticeably in motor function and also in spatial working memory), whereas those least dopamine-depleted, in the ventral striatum, tended to show impairments in behavior that we had come to associate with the ventral striatum (aspects of reversal learning and risky gambling behavior; Cools et al. 2001).

Further studies conducted with consultant neurologist and basal ganglia expert Roger Barker and colleagues, together with Danny Weinberger's group at NIMH, were to show even greater complexity. Thus, a genetic polymorphism associated with the regulation of dopamine function in the PFC (catechol-o-methyl-transferase) conferred on some Parkinson patients, who expressed the *met-met* genotype (associated with high prefrontal dopamine levels) paradoxical cognitive impairments on such tasks as the Tower of London planning task when early in the course and also on L-Dopa medication (Foltynie et al. 2004). It seemed from these studies that too much, as well as too little, dopamine could result in cognitive deficits in Parkinson's disease. Several other lines of evidence supported this dopamine overdose hypothesis; it was also clear that these fronto-striatal impairments did not necessarily predict Parkinsonian dementia, and other evidence now encourages the view that this may be a consequence of an entirely distinct nondopamine (not-striatal) pathology. We thus now have a dual-syndrome hypothesis of Parkinson's disease pathology: the first refers to a dopamine-dependent fronto-striatal component, and the second to another more posterior cortical syndrome possibly related to Lewy bodies and tau inclusions that is especially sensitive to the influence of other chemical transmitter deficits in Parkinson's disease, notably acetylcholine and noradrenaline (Kehagia et al. 2010).

This work on Parkinson's disease was paralleled by other work on neurodegenerative disorders, such as Huntington's disease (e.g., Lawrence et al. 1998) and fronto-temporal dementia (e.g., Rahman et al. 1999), that again had been inspired by our work on experimental animals, especially marmosets. But perhaps the most exciting breakthroughs were provided by our work on the early detection of Alzheimer's disease with Sahakian and John Hodges. Another of the CANTAB tests, visuo-spatial paired associate learning (PAL), turned out to be exquisitely sensitive to the memory impairments observed in early Alzheimer's disease (Swainson et al. 2001). This task had been inspired by several influences, including an early study by Smith and Milner (1981) on object-location memory in patients with hippocampal lesions and by parallel studies on monkeys in Mishkin's laboratory (Parkinson et al. 1988). The basic rationale of the task was to remember the location of several objects, a cognitive capacity apparently requiring the hippocampus, where visual and spatial streams of information converge for potential association. Thus, several boxes on the screen are opened successively one after the other to display a distinct visual icon in each one. Before each icon is displayed in the center of the screen, the subject merely has to touch the white box in which it originally was associated toward the margin of the screen. The task begins with six boxes, but with only two objects to be remembered, before becoming six and then eight objects over a short number of trials. Working in our group, Swainson found that patients with questionable dementia, attending a memory clinic for the first time, were

divided into two groups by this task, some performing normally and others showing impairments as great as those of many early Alzheimer patients (Swainson et al. 2001). Many of these latter patients subsequently were shown to exhibit further deterioration and eventually were diagnosed as having probable Alzheimer's disease. This finding, conducted with the aid of a joint grant held with GlaxoSmithKline provided an enormous boost to the foundation of a company, Cambridge Cognition, to develop CANTAB further. Most recently, Cambridge Cognition was launched on the London Stock Exchange upon the release of a product, CANTAB Mobile, which provides the PAL tests as an objective screening instrument for general practice doctors who have patients complaining of memory loss. In this way, we have endeavored to overcome the two major translational gaps: from animals to humans, and from the research clinic to bedside.

From Actions to Compulsions: Studies of Fronto-Striatal Systems in Neuropsychiatry; Drug Addiction and Other Impulsive-Compulsive Disorders

The CANTAB also provided impetus into our investigations of the functions of the fronto-striatal systems and their chemical neuromodulation. Although Everitt and I continued into our grand overall project of comparing the roles of the major chemical systems into motivational as well as cognitive systems, we were focused especially on apparent parallels and differences in functioning between the ventral and dorsal striatum in the context of drug addiction. Major strides already had been made in this field that promised to provide the most convincing neuroscientific underpinning of all of the neuropsychiatric disorders (with the possible exception of anxiety). We had focused on the role of the projections from the basolateral amygdala to the nucleus accumbens in forming conditioned associations (both appetitive and aversive) that guided behavior (Cador et al. 1989; Killcross et al. 1997) and came to recognize, along with others, that the chronicity of drug exposure in addiction made it highly susceptible to conditioning influences, consistent with much human addiction phenomena. Our early studies, with Athina Markou from San Diego and others, concentrated on redeploying the so-called second-order schedule of reinforcement, an acquaintance with which I had gained in my time at Harvard, by which instrumental responding for drugs, such as cocaine and heroin, is maintained in part by the delivery of brief stimuli associated with the drug infusions. The importance of this procedure is that it enables some measure to be made of the animal's motivation to obtain the drug before the drug is actually on-board, when, naturally, instrumental responding is further exacerbated, especially with drugs such as cocaine and amphetamine that already had been shown to enhance the effects of such conditioned reinforcing stimuli (Arroyo et al.

1998). We initially employed this procedure to establish the roles of the basolateral amygdala and different subregions of the nucleus accumbens (core and shell) in cocaine-seeking behavior (Whitelaw et al. 1996). Later studies with Rutsuko Ito and Dalley also employed in vivo microdialysis to show in well-trained rats that dopamine was released in the nucleus accumbens following cocaine infusion, but not generally during the initial period of receiving only the conditioned stimuli. The most exciting result, however, was that dopamine was released in the dorsal striatum during this phase, almost to the same extent as the drug itself (Ito et al. 2000, 2002). This result, together with others, led to the hypothesis in what is now our most-cited review article that addiction involves a shift of control, initially from the ventral striatum and ultimately to the dorsal striatum (Everitt and Robbins 2005). We speculated that this corresponds to the shift often observed from goal-directed to habit-based learning, which already was surmised from the work of White, Mishkin, Balleine, Graybiel, and others to be mediated by the dorsal striatum, and that addiction also could be understood in this light. Recent reviews have surveyed the relevant evidence one decade on for this hypothesis (Everitt and Robbins 2016). Another important component of the theory is that a gradual loss of top-down control from the PFC over these striatal domains results in the development of compulsive sequences of actions built up from habits (see Figure 4). One important question that we have pursued is whether this loss of top-down control is produced by exposure to the possibly neurotoxic effects of drugs of abuse or, alternatively, whether it is a consequence of individual predisposing factors that could result from genetic or experiential factors. We think that the answer is a mixture of both influences, at least in the case of stimulant abuse.

Earlier developments in our human neuropsychological test battery enabled us to monitor influences of top-down control in decision making relevant to drug abuse and other psychiatric disorders. We were especially interested in cognitive or response inhibitory control mechanisms and had developed several tests in animal and humans to measure these, including the stop-signal reaction time task (Logan et al. 1984), temporal reward discounting, and the so-called Cambridge Gamble Task (Roger set al. 1999a). We also had begun to employ brain imaging methodologies using both fMRI and PET to highlight the neural circuits that were engaged by such tasks in healthy volunteers (Rogers et al. 1999b). A key example was the slowed stop-signal performance of patients with lesions of the inferior frontal cortex, especially in the right hemisphere, that had been shown by Sahakian's outstanding graduate student Adam Aron, working with what were then sophisticated means of measuring the extent of structural loss in different sectors of the frontal lobe employed by Ed Bullmore and Paul Fletcher (Aron et al. 2003). I was astonished at the selectivity of this impairment and its implications, which I think remains central to the debate on the nature of PFC functioning (cf. Aron et al. 2014). Another key paper was

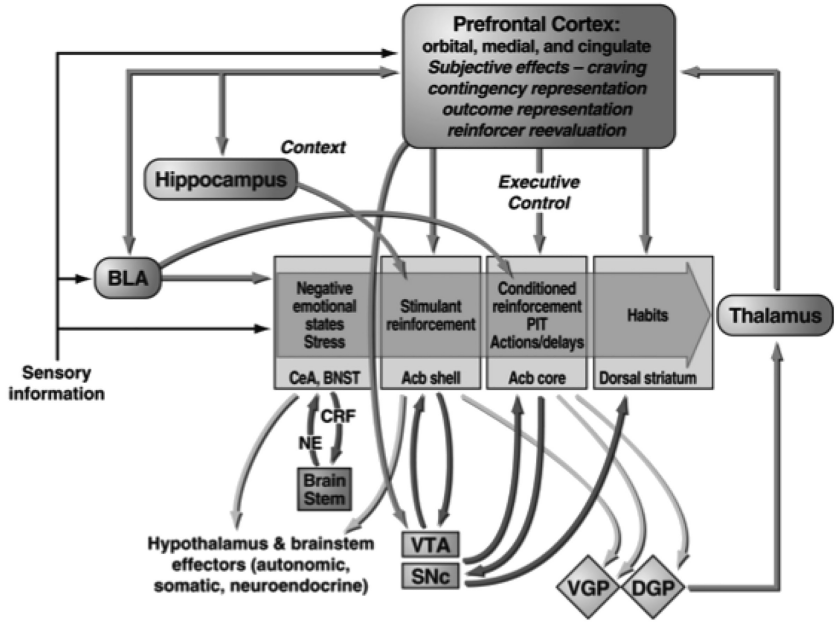

Fig. 4. Neuropsychological scheme to explain stimulant drug addiction as shown in Everitt and Robbins (2005). Note the role of ventral striatum in conditioned reinforcement, the dorsal striatum in habitual behavior, and the prefrontal cortex in top-down control. Reproduced with permission from the publishers of *Nature Neuroscience*.

one with Robert Rogers comparing performance on the Cambridge Gamble Test of patients with frontal lesions and drug abusers, as well as healthy volunteers with transient putative 5-hydroxytryptamine (5-HT) depletion caused by tryptophan depletion, thus mimicking the loss of brain serotonin that has been observed in stimulant abusers post mortem), and showing clear parallels in decision-making impairments (Rogers et al. 1999a).

In rodent experiments, we had shown that basic decision-making impairments were caused even by manipulations of the nucleus accumbens itself. Rudolf Cardinal, with Everitt and myself, showed that damage to the core subregion produced impulsive responding on a temporal discounting procedure for rats that had been pioneered by Evenden (1999); the lesioned rats consistently chose the small immediate reward over the larger delayed one (Cardinal et al. 2001). A later study by Dawn Eagle found that a rat analogue of the stop-signal task was not impaired by similar lesions, although damage to the dorsal striatum was effective in slowing stopping performance (Eagle and Robbins 2003). Thus, it appears that different aspects of top-down control are mediated via different fronto-striatal connections and possibly by distinct neuromodulatory influences. Thus, for example, noradrenergic and serotoninergic drugs appear to exert distinct actions. One finding of especial significance

is that the stop signal reaction time task appears to be rather impervious to effects of serotonin manipulation in both humans and rodents (Eagle et al. 2009). In fact, the classical notion that 5-HT mediates behavioral inhibition has been quite severely constrained by our recent studies (e.g., Winstanley et al. 2004), although this neurotransmitter has been shown to exert ramifying actions in sophisticated areas of social cognition (e.g., Crockett et al. 2010).

Perhaps the most significant finding we have had in this area involved a third form of impulsive responding, the premature responding measure on the rodent 5CSRTT. Dalley had noticed the wide individual variation for this particular measure in Lister hooded rats and discovered that it corresponded to their individual susceptibilities to develop cocaine binge-taking behavior. Moreover, when these high-impulsive rats were screened for their striatal dopamine D2 receptors, which Nora Volkow et al. (2007) had shown convincingly to be reduced in human chronic stimulant abusers, they were shown to be significantly reduced in numbers even though they had not been previously drug exposed (Dalley et al. 2007). The high-impulsive rats were later shown to have compulsive drug-seeking behavior, as indicated by their willingness to experience punishing electric foot-shock in order to earn i.v. cocaine infusions (Belin et al. 2008). These findings suggested that impulsivity associated with low D2 dopamine receptors may be a predisposing factor for stimulant drug abuse, leading to addiction.

To test this hypothesis in humans, we have adopted a number of approaches. Karen Ersche has employed both neuroimaging and behavioral measures in an endophenotype strategy, by which not only chronic dependent stimulant abusers, but also their unaffected sibling probands, have been tested. In several studies, we have been able to show that impulsivity is present in these siblings, whether measured in terms of impulsivity self-rating (Ersche et al. 2010) or by objective tests, such as the stop-signal reaction time task. In addition, the impaired performance in the stop task is associated with reduced integrity of the white matter in the frontal lobe, probably innervating the inferior frontal cortex, which is known to participate in these functions (Ersche et al. 2012). Ersche also has shown that some of the changes in grey matter in the temporal and frontal lobes are not present either in siblings (Ersche et al. 2011) or in recreational stimulant abusers who have not received a diagnosis of substance use disorder, but they may be correlated with the duration of stimulant drug use. This finding supports the concept that frontal control in these patients is compromised both by the predisposing constitution of the drug abusers and also by the effects of the drugs themselves, although whether the latter effects are permanent or reversible remains to be seen. A converging approach has been in the form of a massive, EU-funded prospective study, IMAGEN, which has sought to obtain predictive markers for drug abuse in a large (n = 2,000) population of healthy adolescents, using brain imaging, behavioral, and genetic markers. Intriguingly, the pattern of neural

network activations produced by the stop-signal reaction time task was indeed related to early abuse of nicotine, alcohol, and illicit substances (Whelan et al. 2012).

The studies on drug addiction recently have led us to the more general phenomenon of "impulsive-compulsive disorders," including ADHD and obsessive-compulsive disorder (OCD). Our studies of ADHD stemmed from the original interest in the effects of stimulant drug medication and their apparent cognitive-enhancing actions. This finding that methylphenidate could improve spatial working memory even in volunteering Cambridge students (Elliott et al. 1997; Mehta et al. 2000) suggested to us that the drug was basically a cognitive enhancer rather than remediating a basic deficit, a hypothesis buoyed by our recent findings using PET to measure D2 receptors in adult ADHD (del Campo et al. 2013). Other studies have focused on the relative contribution of the effects of dopaminergic and noradrenergic actions of methylphenidate and their neural location. This has led us to compare other atypical stimulant drugs with methylphenidate, notably atomoxetine, the relatively selective noradrenaline reuptake blocker (Chamberlain et al. 2006), and modafinil, the neurochemical actions of which are quite obscure but have definite cognition-enhancing effects in healthy volunteers on CANTAB tests, such as the Tower of London, and even in patients with schizophrenia (Turner et al. 2003, 2004).

Most recently, I have been investigating OCD with Naomi Fineberg, Sahakian, and others as a prototypical example of compulsive behavior and in comparison with drug abuse and other compulsive disorders. The same notions of dysexecutive control and a drift to habit-based learning have permeated our thinking on this devastating condition, which bears relationships with anxiety disorders, schizophrenia, and depression as well as behavioral addictions. Thus, Sam Chamberlain in our group has shown that ed attentional set-shifting is significantly impaired in the unaffected siblings of OCD patients as well as in the OCD patients themselves, suggesting a general tendency to rigid behavior (Chamberlain et al. 2007). Additionally, both siblings and OCD patients exhibit reduced orbitofrontal activation during reversal learning (Chamberlain et al. 2008), which is consistent with our earlier findings of deficits in reversal following excitotoxic lesions to such regions or depletion of serotonin to those same regions in marmosets (Clarke et al. 2004). These reductions may contribute to OCD symptoms and may be remediated in patients following treatment with high doses of selective serotonin reuptake inhibitors. Impairments in goal-directed behavior to the apparent advantage of habit-based learning have emerged by applying the principles of diagnosing habits using reward devaluation methodology that originally were proposed by Anthony Dickinson (1985), whether applied to appetitive or aversive learning (Gillan et al. 2011, 2014). Our most recent attempts are to relate these behavioral findings to the operation of discrete fronto-striatal systems using a range of neuroimaging

paradigms. Overall, and consistent with our previous CANTAB strategy, we are keen to continue to employ new behavioral paradigms and neuroimaging methods to better define phenotypes within neuropsychiatry, consistent with our studies of the functions of neural systems in experimental animals. This work may result in the fractionation and neural dissection of several neurobehavioral constructs into further components on the way, including impulsivity and compulsivity.

I perceive some persistent themes in my intellectual interests from the earlier parts of my career; I am still fascinated by the notion of loss of control over subcortically mediated behaviors and their adaptive motivation, if any. These behaviors extend from stereotypies to deficits in cognitive rigidity and habit-based learning, representing an apparent hierarchical organization over cognitive and behavioral output that appears to dominate the output of the frontal lobes mediated by structures such as the basal ganglia, under the differing states of arousal or activation reflected by environmental influences and dispositions imposed by the interplay of the major ascending monoamine transmitters. I suspect that neuroscientists such as myself never lose intellectual commitment to anything they once began to study; they simply add them into an ever-increasing and intoxicating intellectual mix into which they can but hope to embroil and fascinate their younger colleagues.

Epilogue

The bare bones of my career are summarized at the start of this article; they do not necessarily represent the highlights. It was wonderful, however, to be appointed full professor at Cambridge in 1997 at the same time as Everitt and also, for our collaboration, to be jointly honored by the American Psychological Association in 2011. Other highlights have included being elected to a fellow of the Royal Society, the most prestigious of the U.K. scientific bodies. I remember with excitement the Discussion Meetings I helped to organize for the Royal Society on Prefrontal Cortex Function and the Neurobiology of Drug Addiction in 1996 and 2009 and the accompanying edited books. I also have much enjoyed editing the journal *Psychopharmacology* since 1980. My service to "medical research" and U.K. Research Councils was marked by an appointment as Commander of the Most Excellent Order of the British Empire in 2012. A crowning honor was the award of the Grete Lundbeck Brain Prize with S. Dehaene and G. Rizzolatti in 2014.

Acknowledgments

I acknowledge over the course of some 40 years the support of the Department of Experimental Psychology (now Psychology) and its esteemed faculty who have provided continuous intellectual stimulation and inspiration: I was

honored to be elected to be head of department in 2002, succeeding the luminaries Bartlett, Zangwill, and Mackintosh. I also acknowledge the generous and continuous support of the MRC and Wellcome Trust, including the formation of the Behavioural and Clinical Neuroscience Institute, with Ed Bullmore as clinical director. I am grateful to generations of Cambridge undergraduates, graduates, and postdocs who have been part of the lab. It has not been possible to acknowledge all of their individual contributions to my work; I have had to be selective in describing its main themes and my failure to incorporate reference to their own often independent and brilliant contributions in no way implies that I regard their own efforts as being of any less significance or importance to me.

Finally, I acknowledge with extreme gratitude the support of my extraordinary partner Barbara Sahakian, who has had an eminent career in her own right, while also bearing the major burden of family life and children. Our daughters Jacqueline and Miranda are now both graduate students in the field of neuroscience, although working in areas quite separate from behavioral and cognitive neuroscience.

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