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Edited by Warrick J. Brewer, David Castle and Christos Pantelis

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## Olfaction and the Brain

Olfaction and its relation to mental health is an area of growing interest, evidenced by the 2004 Nobel Prize in Physiology or Medicine being awarded for discoveries relating to odorant receptors and the organization of the olfactory system. Olfaction is of particular interest to specialists seeking a fuller understanding of schizophrenia. Clear deficits in the sense of smell could predict schizophrenia in apparently unaffected individuals.

In this highly timely book, Warrick Brewer and his team of experts set out our current understanding of olfaction and mental health, relating it to broader principles of neural development and processing as a foundation for understanding psychopathology. The neuro-pathological, neuropsychological and neuropsychiatric aspects of olfactory function and dysfunction are all covered (drawing on the latest neuroimaging techniques where appropriate), and indications for future research and applications are discussed.

This will be a source of state-of-the art information and inspiration to all mental health professionals.

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# Olfaction and the Brain

Edited by  
Warrick J. Brewer,  
David Castle and  
Christos Pantelis

with a foreword by Peter Doherty  
Peter Doherty jointly won the Nobel Prize in  
Physiology or Medicine in 1996 for  
his work in immunology.



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Contents

|                             |                 |
|-----------------------------|-----------------|
| <i>Foreword</i>             | <i>page vii</i> |
| <i>Preface</i>              | <i>ix</i>       |
| <i>List of Contributors</i> | <i>xiii</i>     |

Section I   **Neurology, Neurophysiology and Neuropsychology:  
Olfactory Clues to Brain Development and Disorder**

|   |   |     |
|---|---|-----|
| 1 | Structure and Function of the Olfactory System                              | 3   |
|   | Alan Mackay-Sim and Jean-Pierre Royet                                       |     |
| 2 | Olfaction and the Temporal Lobes  | 28  |
|   | Jelena Djordjevic and Marilyn Jones-Gotman                                  |     |
| 3 | Role of the Insula in Smell and Disgust                                     | 50  |
|   | Maïke Heining and Mary Phillips   |     |
| 4 | Olfaction and Memory  | 65  |
|   | Mikisha Doop, Christine Mohr, Bradley Folley, Warrick Brewer and Sohee Park |     |
| 5 | Olfactory Neurogenesis: A Window on Brain Development                       | 83  |
|   | François Féron, Richard McCurdy, John McGrath and Alan Mackay-Sim           |     |
| 6 | Olfactory Processing and Brain Maturation                                   | 103 |
|   | Warrick Brewer, Christos Pantelis, Cinzia De Luca and Stephen Wood          |     |
| 7 | Probes of Behaviour Regulation: Olfactory Models in Addiction               | 119 |
|   | Dan Lubman, Murat Yücel and Warrick Brewer                                  |     |

Section II   **Social Functioning: Role of Evolution, Genetics and Gender**

|   |  |     |
|---|--|-----|
| 8 | Primate Olfaction: Anatomy and Evolution | 135 |
|   | Timothy Smith and James Rossie           |     |

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Frontmatter  
[More information](#)

| vi   | Contents   |     |
|--|--|-----|
| 9  | Genetics and Family Influences on Olfaction: A Focus in Schizophrenia  | 167 |
|  | Raquelle Mesholam-Gately and Larry Seidman                             |     |
| 10   | Sex Differences and Olfactory Function                                 | 183 |
|  | Kim Good and Lili Kopala   |     |
| 11   | The Role of Pheromones and Chemistry: Lessons from Comparative Anatomy | 203 |
|  | Michael Stoddart   |     |
| 12   | The Impact of Olfaction on Human Social Functioning                    | 220 |
|  | Dolores Malaspina, Cheryl Corcoran and Nora Goudsmit                   |     |
| <br><b>Section III Assessment and Disorders of Olfaction</b> |  |     |
| 13   | Assessment of Olfaction  | 235 |
|  | Richard Doty   |     |
| 14   | Olfactory Impairment in Neuropsychiatric Disorders                     | 259 |
|  | Christos Pantelis and Warrick Brewer                                   |     |
| 15   | Olfaction in Parkinsonian Syndromes                                    | 279 |
|  | Christopher Hawkes   |     |
| 16   | Olfaction in Psychosis   | 296 |
|  | Paul Moberg and Bruce Turetsky   |     |
| 17   | Olfactory Hallucinations   | 322 |
|  | Dennis Velakoulis  |     |
| 18   | Delusions of Body Malodour: The Olfactory Reference Syndrome           | 334 |
|  | Katharine Phillips, Craig Gunderson, Uschi Gruber and David Castle     |     |
|  | <i>Index</i>   | 355 |

# Foreword

While there is still much to be discovered in many areas of biology, perhaps the greatest challenge is to understand the human brain, to illuminate the mind/brain duality. Unlike philosophy and religion, which can sometimes regress into the scholasticism that so limited human advancement and well-being through the dark ages, science is evidence-based and moves forward by exploration, hypothesis and experiment. Science depends on objective measurement. No matter how bright the individual research investigators may be, the conclusions that are reached can only be as good as the underlying observational systems. How do we measure the workings of the brain?

The analysis of brain function has, of course, been enormously enhanced in recent years by technologies like Magnetic Resonance Imaging (MRI) and the capacity to record various electrophysiological outputs. What then becomes important is the source and nature of the input stimuli that induce distinctive neural response patterns. When it comes to such access, the senses of sight, touch and smell provide, of course, primary, natural ‘windows’ to the brain. At least in the consciousness of medical scientists, smell came to the fore in late 2004 when Richard Axel and Linda Buck were awarded the Nobel Prize for Medicine, for ‘their discoveries of odorant receptors and the organization of the olfactory system’.

Though I work with immunity, the other great, complex biological system that mediates specific recognition of (and appropriate responses to) external stimuli, olfaction is an area that has long interested me. A substantial component of my research over the past 30 or more years has focused on the major histocompatibility complex (MHC), the region of the higher vertebrate genome that encodes the strong transplantation antigens, the targets of organ graft rejection. When our own (self) class I MHC molecules are modified by the attachment of a short, ‘non-self’ peptide (8–10 amino acids) from an infecting virus or some other pathogen, any cell expressing this ‘altered-self’ complex is seen as ‘foreign’ by the ‘hit men’ of the immune system, the cytotoxic T lymphocytes (CTLs) that patrol the body looking for evidence of invasion and damage that must be neutralised in order to maintain good health. Perhaps to avoid any possibility that a virus or bacterium may evolve by mutating to defeat

**viii** Foreword

this immune surveillance mechanism, the class I MHC molecules are enormously diverse (or polymorphic) within any given mammalian species.

What amazed everyone in the transplantation field when the first results were reported in the late 1970s is that animals that rely heavily on the sense of smell, such as mice, rats and police tracker dogs, can readily distinguish between individuals of their own (or different) species on the basis of class I MHC molecular diversity. Experiments using a ‘sweaty T shirt test’ have shown that the same odorant-based discrimination process works in humans. Furthermore, an ‘electronic sniffer nose’ developed originally to detect air-borne chemical ‘signatures’ emitted by the explosives in land mines can also be programmed to tell the difference between various blood and urine samples from people (or mice) of different MHC types. You will be familiar with this technology if your portable computer has ever been ‘swabbed’ at an airport security checkpoint, though the technician is looking for evidence of a bomb and is not (we hope) trying to classify you by your particular body odour!

The mechanism underlying olfactory MHC ‘typing’ is still far from clear, though like the electronic nose, it clearly depends on the recognition of various volatile compounds. Even more surprising, recent studies have shown that other areas of the MHC are coding for some of the odorant receptors that determine pheromone recognition. Could the MHC polymorphism that is so important for immunity simply be a reflection of a much older (in evolutionary terms) process based on odorant-determined sexual preference? (See, ‘On the Nose: shared themes for the sensory and immune self’. *Nature Immunology* 4:1043–45, 2003)

The present volume is particularly fascinating as it links olfaction with a broad range of insights and observations based on molecular neurobiology, neurology, psychiatry and psychology. As an immunologist who is also intrigued by brain function and by philosophical ideas that incorporate findings from contemporary neuroscience, it seems to me that a big question facing us concerns how we deal with modes of behaviour that are fundamentally determined by genetics and physiological response patterns, especially if these should happen to involve consequences that are considered to be inappropriate or even anti-social. Because the sense of smell can be used to access neural mechanisms in ways that are non-invasive and unlikely to upset those who are threatened by medical procedures, fundamental and clinical research that both probes and utilizes olfaction has the potential to help humanity resolve some of these difficult issues. This widely ranging book provides a useful and informative compendium that allows the general science and informed lay reader to access an important, complex and fascinating field of human enquiry.

Peter C. Doherty

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## Preface

This book provides a timely and up-to-date overview of how we understand olfaction, its neurobiological basis as well as providing an evolutionary perspective. The neuropathological, neuropsychological and neuropsychiatric aspects of olfactory function and dysfunction are considered, drawing on the latest neuroimaging techniques, where appropriate. A strong focus is on schizophrenia, as this disorder represents compromise of the unique and complex interplay between aspects of the developing ‘self’ that include biology, psychology and the environment – all of which involve olfaction. The intent is to illustrate the advantages of extending our understanding of this primary sense, which in turn widens our knowledge of broader principles of neural development and processing as a foundation for understanding psychopathology. The overall aim is to elevate the often under-estimated sense of smell to a level of significance that should stimulate readers to consider olfactory models and principles of function as a guide to broader research paradigms, and should also encourage wider use of olfactory assessment in neurological, psychiatric and psychological settings during the process of diagnosis and assessment.

Chapter authors are internationally recognised experts in their respective fields who have also demonstrated their ability not only to understand and enhance our knowledge of olfaction within the perspective of a wide variety of broader clinical and research programs, but to relate their knowledge of complicated neurobiological processes in a readable and accessible manner.

Section I sets the foundation for the rest of the book, with Chapter 1 providing a detailed description of the structure and function of the primary olfactory system (Mackay-Sim and Royet). This chapter encompasses an overview of how the chemical properties of odourants are encoded into neural activity. In addition, these authors describe the regions of neural activity that are involved in the various aspects of olfactory processing. This chapter includes a detailed exploration of the olfactory epithelium and the olfactory bulb and provides the



link between such basic biology and olfactory perception. In Chapter 2, Djordevic and Jones-Gotman evolve this further, with a particular focus on temporal lobe functioning and olfaction. Their work derives from their studies in epilepsy in Montreal, with an emphasis on neuroimaging techniques. Based on their functional imaging work in London, Heining and Phillips (Chapter 3) examine more intricate aspects of the relationship between components of olfaction and olfactory pathways and socio-biological behaviour. They provide an intriguing account of the role of disgust and the amygdala in relation to olfactory stimuli, and discuss the functional implications of compromise of normal reactive emotional responses to aversive stimuli and the relevance to understanding mental illness. Doop, Mohr, Folley, Brewer and Park explore the relationship between the higher cognitive processes and olfaction in Chapter 4. The evocative nature of olfactory memory particularly, and its role in the re-creation of the self, are reflected in this chapter to draw the reader into a deeper appreciation of this most romantic of the senses.

An aim of Section I is to reflect novel methods to explore the hierarchical nature of olfactory stimulus processing from sensory experience in olfactory epithelium through to emotional processing in the limbic system and higher order olfactory information processing in frontal regions, and to understand these processes within a neurodevelopmental framework. Féron, McCurdy, McGrath and Mackay-Sim describe in Chapter 5 how careful exploration of the process of neurogenesis of the olfactory bulb might uncover more general principles that help us understand neurodevelopment generally, and neuropsychiatric disorders more specifically – particularly schizophrenia. Their work is based on a unique Australian research programme that relies upon examination of olfactory neuro-epithelial cultures that are gained from nasal biopsy. Brewer, Wood, de Luca and Pantelis extend this thesis in Chapter 6, and consider the various aspects of olfactory processing in normal individuals and in pathological states within a neurodevelopmental perspective. Based on their work over the last decade, they propose that the nature of olfactory abnormalities and the brain regions involved in disorders in early life need to be understood by considering the brain maturational stage at the time of onset of such disorders. These authors highlight the importance of understanding the maturation of various aspects of olfactory function and of relevant fronto-limbic circuitry, and particularly emphasise the importance of maturation of higher-order olfactory function (implicating orbito-frontal neural systems) in understanding the nature of olfactory disturbances in disorders of adolescence and early adulthood.

In the final Chapter of Section I, Lubman, Yücel and Brewer describe a model of orbito-frontal cortex (OFC) functioning and associated behaviour, and outline how OFC compromise would be expected to result in reduced ability

to regulate affect and in dysfunctional behaviour, such as addiction. While the focus in this chapter is more on disordered behaviour rather than olfaction *per se*, the purpose is to stimulate implementation of less-obvious models of research in domains that might usefully exploit tasks of olfactory ability and their differential timing of maturation over the course of development. Here, the aim is to elucidate the nature and course of those same disorders with an emphasis on early detection.

Section II traces influences on the development of olfaction in humans in the context of evolution, with an emphasis on communication. The roles that genes, gender and pheromones play in the foundation of olfactory function are described. An evolutionary perspective on the adaptive nature of primate olfaction and anatomy by Smith and Rossie (Chapter 8) sets the scene for the ensuing chapters that outline the importance of olfaction as a facilitator of social interaction. Functional implications of skull and nasal structure in primates are described. Evidence of adaptation is drawn from the nervous system, with reference to olfactory progressive diminution from its state in other mammals to that in primates, particularly in the fields of comparative neuroanatomy and neurophysiology. In terms of genetic implications on olfaction, Mesholam-Gately and Seidman describe family and high-risk schizophrenia studies (Chapter 9) to demonstrate how disordered olfactory functioning might provide clues to the genetic foundations of complex neuropsychiatric diseases in general and, in particular, biological markers for schizophrenia. In a similar context, Good and Kopala (Chapter 10) review sex differences in olfactory ability, and reinforce the notion of how important odour cues carry information regarding fertility status or genetic make-up. Implications of genetic influences on olfactory function from the perspective of gender, and associated relevance to psychiatry, are also outlined. How such differences may impact on increasing our understanding of psychopathologies such as schizophrenia is also explored. In further detail, Stoddart (Chapter 11) expands our understanding of the nature of pheromones and chemistry via comparative anatomy. He includes a description of recent controversial findings regarding the vomeronasal organ. This chapter provides a historical perspective on understanding the role of chemical messengers in animals and humans. Returning to implications of these primal aspects of social communication for humans, understanding olfaction in the context of social behaviour is extremely pertinent to the human condition. For most mammals, social hierarchy and territory are recognised by odour, and smell plays a key role in identifying life-enhancing stimuli and enemies and in determining safety from danger. The brain circuitry involved in emotional processing and olfactory function is overlapping and olfactory information is unique in comparison to other sensory modalities because of its direct input

to the prefrontal cortex. Malaspina, Corcoran and Goudsmit (Chapter 12) provide a fascinating review of how this understanding of neural circuitry and the behaviour it mediates facilitates social communication via pheromones.

Finally, Section III focuses on specific assessment and detection of disorders of olfactory function in neuropsychiatric disorders. Doty (Chapter 13) describes the utility of standardised assessment of olfactory function, with particular emphasis on sensitivity and specificity across a range of disorders that manifest reduced olfaction. Specific reference to available bedside tests is included. Pantelis and Brewer (Chapter 14) provide an account of olfactory compromise of neuropsychiatric disorders, including early neurodevelopmental disorders and late neurodegenerative conditions, while Hawkes (Chapter 15) provides a more detailed account of the nature and extent of olfactory deficits in disorders of the striatum, particularly neurodegenerative disorders. The emergence of olfactory deficits at various stages of each illness and their neurobiological and clinical implications is discussed in these two chapters. In Chapter 16, Moberg and Turetsky review olfactory disorders in schizophrenia. The focus on olfactory function in neuropsychiatric disorders is continued by Velakoulis (Chapter 17), where structural and functional imaging research concerning olfactory hallucinations is explored, with particular focus on pathological conditions of the temporal lobe. This includes a historical analysis of the epilepsy and psychosis literature that is associated with olfactory hallucinations. In the closing chapter, Phillips, Gunderson, Gruber and Castle (Chapter 18) review the literature on the Olfactory Reference Syndrome (ORS) – an under-recognised type of delusional disorder that has been described for more than a century. It consists of a false belief that one emits an offensive body odour and is often accompanied by prominent delusions of reference and repetitive behaviours aimed at checking or reducing the perceived odour. This chapter discusses this syndrome’s history, clinical features, prevalence, treatment response, possible pathogenesis and nosological status.

It is hoped that this book will stimulate clinicians and researchers across the neuroscientific disciplines to consider the unique role and functional implications of olfaction. We are only at the beginning of unlocking the mysteries of our most primal sense, and we trust that our authors trigger interest in further exploration. We fully expect that such interest will expand our appreciation of this fascinating window to the mind.

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