Vol 13, No.2 April 2011

Chemo Sense

EDITORIAL

Joy and a whiff of sadness

By Graham Bell
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The earthquakes and floods in our Australasian region have been eclipsed by the greater tragedies in Japan.

As we are an international community of scientists and technologists, few will not know someone caught up in these events. *ChemoSense* expresses heartfelt sympathy for all concerned.

By contrast to images of wreckage and chaos, Peter Brunjes takes us on a soothing and personal guided tour of the olfactory forebrain and examines the idea that mammalian olfaction must be "simple" because it is common to the most ancient forms of animal life. Peter's joyful

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The Smelling Brain

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If you read much about olfaction it won't take long before you encounter the notion that the sense of smell is " one of the first" sensory systems, a "primordial" and "primitive" modality that has been present for eons and is found in all animals from the simplest to the most complex. Olfaction, then, must be a really simple system then, right? It should be easy to understand since it has been around for so long and is fundamental! Below we will take a brief look at the basic anatomical organization of the sense of smell in mammals. In order to describe this "simple" sensory system in a simple way, we will try to avoid too many details and references (but answers are available just a few clicks of a mouse away!) and just stick to the major ideas. Here we go!

A: The Receptors

Every sensory system has "sensory neurons" (or receptor cells). These cells detect stimuli of interest and react by producing the electrical disturbances that are the means of communication in the nervous system. For example, in the visual system there are rods, which detect just the presence or absence of light, and three kinds of cones (blue, green and red-yellow) that detect color (the wavelength of the light). The auditory system only has a

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www.chemosense.info www.e-nose.info
ISSN 1442-9098

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narrative style does much to make your journey easy and rewarding. At first you can see order in the complexity, but as the "river" you are following into the interior, repeatedly divides into little-known regions, you soon learn that the brain mechanisms of olfactory experience are anything but simple.

For the first time in its short history, AACSS will be meeting in New Zealand in December 2011. Contact the organisers now to suggest speakers and conference content: www.aacss.org ■

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single kind of cell ("inner hair cells"). These cells code different tones on the basis of where they are in the ear, and thus how fast they vibrate. Pretty simple! These two major modalities for humans only have a couple of choices of sensory neurons, yet are capable of detecting the richness of the sensory world.

What about the nose? The answer turns out to be rather complicated. Of course there are cells that respond to chemicals that come into the nasal cavity with the air you breathe, but there are also cells that respond to many other things including water-borne odors, the "feel" of odors (for example, menthol smells "cool"), carbon dioxide and even some receptors that respond to bitter tastes! Most of the cells extend small, hair-like cilia into the mucous layer that lines and protects the airways (Fig. 1B). The cilia have specialized proteins that detect differently shaped molecules through a key-in-the-lock sort of mechanism. One can think of these detectors as being like any of the multitude of other kinds of chemical receptors throughout the body. For example, many drugs are just chemicals that are designed to fit into one of the body's molecular detectors. When the key fits into the lock the effect is to either activate or inactivate the assembly (e.g., turn off pain, wake you up). Olfactory receptors can be seen as having the same kinds of general pharmacological dynamics, with some molecules activating the receptor cells (agonists) or inactivating (antagonists) the cells. Activated receptors are coupled to proteins that induce an electrical disturbance in the cell, and then this message is carried to the brain. The sequences by which the receptors induce these changes (the "signaling cascade") are a very hot area of research, but we are going to avoid these complexities and just point out that several different pathways have been described. Suffice to say, a variety of "g-protein-coupled" receptors have been found which may activate one of several series of intracellular changes that ultimately open one of several different ion channels, each with different kinetics including cyclic nucleotide gated channels, calcium activated chloride channels, TRP channels, etc. The results are that the messages that different cells generate might be different:for example, they might be fast or slow, brief or extended, etc., but messages nevertheless.

We see millions of different colors with just three types of cones. We can also detect a huge number of different odors (though how many is uncertain: there are tens of thousands of airborne molecules, but not all of them are detected, and thus have a smell). How many olfactory receptors are there? For starters, most mammals have 5 different regions in the nose in which chemosensory cells reside (Fig. 1A). In order from smallest in area to the largest, they are the:

a. Grüneberg ganglia. This is a small collection of neurons found near the entrance to the nasal cavity that appears to respond to alarm pheromones and cold temperatures;

b. Septal organ of Masera. A patch of cells found on the cartilage that separates the left and right nasal cavity (the "nasal septum") with a unique morphology and different connections. Relatively little is known about the region's function - see review in *ChemoSense*, 2005,7(2);

c. Chemosensory endings of the trigeminal nerve. The trigeminal, or fifth cranial nerve, brings touch, pain and temperature information from the face to the brainstem. Trigeminal fibers are widely distributed in the nasal cavity, and are sensitive to

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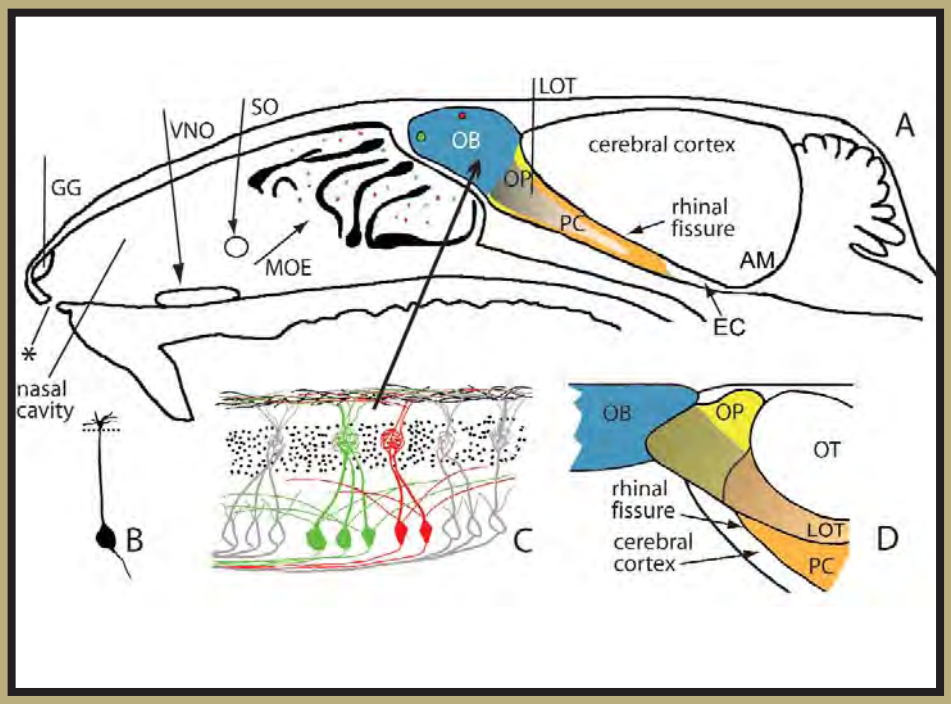

Figure 1

Panel A is a schematic diagram of the olfactory system of a rodent. Air enters the nasal cavity through the nostril ("external naris") on the left (asterisk). As it travels through the airways, molecules come into contact with the sensory neurons located in a number of structures including the Grüneberg ganglia (GG), vomeronasal organ (VNO), trigeminal fibers (scattered throughout the cavity), septal organ of Masera (SO) and, in the back third of the nasal cavity, the main olfactory epithelium (MOE) located on complex leaves of cartilage known as nasal turbinates. The MOE contains millions of sensory cells. The sensory neurons in the region have a tuft of cilia extending into the airways (Panel B, above the dotted line) that contain the receptor molecules for odor detection. Each cell expresses only one variety of receptor molecule; two types are represented in Panel A by red and green dots. The cells send an axon through the thin bone behind the nasal cavity and into the olfactory bulb (OB, blue) of the forebrain. Panel C shows a simple diagram of the OB. Incoming sensory neuron fibers in the outer layer of the OB (top) segregate by olfactory receptor type (e.g., red and green) and form a knot of terminals known as a glomerulus. Second order cells (mitral and tufted cells) receive the information from a single glomerulus. All axons then bundle together to form the lateral olfactory tract (LOT, bottom of Panel C). The right side of Panel A depicts the higher olfactory processing regions from the lateral side; Panel D shows the same area from the bottom of the brain. The LOT forms a conical-shaped tract on the surface of the brain, travelling first over the olfactory peduncle (OP, yellow) and then the piriform cortex (PC, orange). OT= olfactory tubercle; EC= entorhinal cortex; AM= amygdala, which is buried deep in the temporal lobe of the cerebral cortex.

irritants (e.g., sulfur, vinegar, menthol) as well as other odors. Some trigeminal endings have receptors similar to those seen in the tongue (e.g., T2R "bitter-taste" receptors);

d. Vomeronasal organs (VNO). These tube-shaped ducts are found in the anterior nasal cavity nestled against the floor of the septum. In many animals they open near a duct that communicates with the top of the mouth, and as such the organs are thought to "smell" chemicals in solution in the mouth. In the VNO there are two major classes of receptors (V1R and V2R) each of which can have around 100 different kinds of receptors, as well as other small families (e.g., 3-7 formyl peptide receptors). The organ innervates a special region known as the "accessory olfactory bulb" and is thought by some to be involved in perceiving "pheromones".

e. "Main olfactory epithelium." The largest class of olfactory sensory neurons is found in the posterior third of the nasal cavity. Linda Buck and Richard Axel won the Nobel Prize in 2004 for uncovering a family of genes that encodes the proteins that function as the chemical receptors in this area. It turns out that that the family of genes is one of the largest in the genome: mice and rats have about 1000 different olfactory receptors, humans have over 300. Recently, other kinds of receptors have also been discovered, for example the "GCD" receptors. Each olfactory sensory cell expresses only one receptor protein, and cells that express the same gene are spread across the mucosa, doubtlessly so that if an odorant molecule falls in any region it can be detected (Fig. 1A).

In summary, so far: there are 5 different systems that encode "smell". Within these regions there are a very large number of different kinds of chemical receptor proteins. When activated, the receptors can feed into different signaling cascades. Activated cells from different regions innervate different areas in the brain (trigeminal to the back of the brain, the remainder to the olfactory bulb in the front). So, things are getting complex. Maybe we should keep it simple and focus on one—the "main" olfactory system?

B: First Processing Station. The Olfactory Bulb

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Initial processing in the visual system is done at the back of the eye in the retina, where a spatial map of the visual world is established and strictly maintained. The auditory system's first processing stage is in the brainstem where a refined frequency map is evident: low tones are managed in one region, high tones in another. The main olfactory system's first stop is in the olfactory bulb and, lucky for us, it also appears to have a well-organized map of the olfactory world! Of course, there are the inevitable complexities. Recall that each sensory neuron in the mucosa expresses a single olfactory receptor. Incoming axons from all of the sensory neurons expressing a single molecular receptor bundle together in the outer layer of the olfactory bulb and then coalesce into one or two balls of axons and terminals known as glomeruli (one on the medial and the other on the lateral side of the bulb, Fig. 1C). Mice have around 2000 glomeruli.

Much attention has been given to mapping glomerular function in an attempt to unravel a potential odor code map. However, it may not be as easy it is seems: there are always subtleties and problems. For example, odorant receptor molecules are not specifically tuned to one odor. One way of thinking of them is that they recognize a portion of a molecule (remember the sticks and colored balls of Chemistry class?), like a carbon chain of a particular length, a ketone group, or some other chemical motif. Since most molecules are combinations of these features, a single molecule might be capable of binding to several different receptor proteins, and thus activating several glomeruli, and a single receptor protein would be capable of detecting many kinds of molecules. We will ignore the effects of odor concentration and time (olfaction is an inherently timed sensory modality since odor delivery is tied to the movement of air in the sniff cycle) but they are important factors as well. After all is said and done, it seems established that the glomeruli parse the incoming data stream from the nose into separate channels.

Aha! Order in olfactory processing! And the order continues! Information processing seems to occur in "columns" in the olfactory bulb, much like those seen in the retina (Fig. 1C). There are connections between glomeruli that act to sharpen signals, so a strongly activated glomerulus could inhibit its neighbors and thus stand out from the background. Information in each glomerulus is delivered to two kinds of relay neurons, known as tufted and mitral cells. A second network of inhibition allows activated relay neurons to "silence" weakly functioning neighbors, once again sharpening the column of activation. These relay cells take the signal to other areas, with the basic distinction that the tufted cells project to more "local" targets only (e.g., the mirror set of glomeruli in the second map of the same olfactory bulb, to more anterior targets in the forebrain) while the mitral cells send long processes. Of course, the inevitable disclaimer must be made: things are more complicated than they might seem (e.g., the wiring of the bulb is more complicated, the glomerular layer has several cell types, and deeper regions of the bulb do as well with oddly named cells like "Blanes" and "Van Gehuchten" cells, the issue of spatial vs. temporal codes needs to be resolved, etc). But really, these complexities are well beyond our scope. It is important that we end this paragraph with the optimistic note that there is order in olfactory processing and that it is possible that there are separate channels for different odor qualities. Mainly that optimism is important because it is about the last time we see it: chaos lurks!

C: Higher Processing Stations

Vision and audition have roughly similar secondary sites of processing. Both the retina and auditory regions in the brainstem that initially process sound information manage to innervate the thalamus, which subsequently sends a spatially ordered map of the visual or auditory world to the cerebral cortex. Each system appears to function through "hierarchical" processing; at each progressive synapse a more complicated representation of the information is built. As a result, the cortex does not just process points of light or individual sound frequencies; it is involved in more complex tasks like shape or voice recognition. What about smell?

It seems to be almost totally different. The axons of the tufted and mitral cells collect together to form the lateral olfactory tract, which carries the information processed in the bulb to regions of the ventral forebrain collectively referred to as "olfactory cortex" (Fig. 1D). It is called "cortex" because it is on the surface of the brain and has layers, but it has fewer layers than the cerebral cortex (2-3 vs 6) and as a result, is less complicated. (An interesting issue currently being examined is to determine just how similar these cortices are in organization and function. Is olfactory cortex a primitive progenitor of the "real" cortex, or just different?). At this point the story begins to get messy; there are many areas that receive olfactory input so there are a lot of names and divisions with subdivisions, etc. But let's just keep a

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smile on our faces and stick to the big points.

1) The area behind the olfactory bulb is called the "olfactory peduncle" (Fig. 1A, D). It contains several small zones about which relatively little is known (e.g., the "ventral tenia tecta" and "dorsal peduncular cortex") and a larger one known as the anterior olfactory nucleus ("AON"; sometimes referred to as the anterior olfactory cortex). We are just starting to understand its organization and function, but it seems to be quite important in coordinating olfactory information flow on the left and right sides of the brain. People can localize sights and sounds in space by comparing the inputs to the left vs right eyes or ears. People can do the same thing with odors. For example, people can sniff their way through grass to find chocolate (Porter et al., 2007)! The AON has two regions. One, known as "pars externa", sends information from one bulb to the other on a point-to-point basis, and is therefore involved in coordinating processing in the two structures. Unfortunately, pars externa is the end of the easy part of the story as it is the last region where we see obvious, strict spatial order in the system. We will come to the other portion of the AON (pars principalis) shortly.

2) Just behind the olfactory peduncle there are two more large structures. On the inside (medial) is a structure known as the "olfactory tubercle" (Fig. 1D). Not a lot is known about the area, but two facts are apparent. First, it is a portion of the "ventral striatum", a processing system that is quite similar to the "basal ganglia". You might have heard that last term because problems in the area lead to maladies like Parkinson's disease and Huntington's chorea. The basal ganglia is involved in regulating a region in the thalamus, and thus controlling processing in the cerebral cortex. The olfactory tubercle is involved in a quite similar circuit. Second, processing in the tubercle is complex; there are cells there that respond, for example, to both sounds and smells! The integration of information across sensory systems is another very important area of study that is receiving more and more attention. An example of such integration would be "flavor"; the combination of the taste, smell and touch (e.g., crispy, hot or cold) of a stimulus.

The second area is lateral, on the outside of the forebrain, and is known as the piriform or primary olfactory cortex (Fig. 1A, D). Both the piriform cortex (PC) and pars principalis of the AON share roughly similar structures; while the PC has 3 layers and pars principalis has only two, both have many of the same cell types. Recall that in the visual and auditory systems "higher" processing areas preserve the maps established in early in the processing streams. For example, if you expose an animal to a series of lights in different regions of the visual world or sounds of different frequencies, you will find lawful patterns of activation in higher brain regions indicating that these features are spatially mapped. Neither of these olfactory region exhibits such simple "topographical coding"; exposure to various odorants yields overlapping and distributed activation of cells with no detectable simple patterns. So much for order! One idea is that the regions act as "content addressable memories", and, as such, allow the system to have complex processing. For example, imagine a complex sensory image in any modality (e.g.; a familiar picture like the Mona Lisa, a musical phrase, or a complex odor like coffee). You need not experience the complete stimulus to recognize the "entire" picture; a brief glance of an enigmatic smile might bring back the memory of the painting, a snippet of tones might remind you of the musical phrase, or a whiff of air might allow you to detect enough odors to invoke a desire for a "grande skinny peppermint mocha latte". Complex processors using these strategies can fill in gaps in an array of inputs to allow whole patterns to emerge.

Another feature of the piriform cortex is that due to its connections it is capable of moving past simple odor perception to placing an odor into a context. For example, the piriform cortex has connections with the amygdala, a region where the processing of emotional information takes place, and both direct and indirect connections with the cerebral cortex (technically the "orbitofrontal cortex") wherein higher cognition resides. Therefore, the piriform cortex sits in a circuit where smell, emotions, and cognition can be integrated.

Almost done! The lateral olfactory tract fibers project onward to two final regions. One is the amygdala (and the region immediately around it which is known as the "periamygdaloid cortex"). These connections provide a means by which the olfactory system can notify the amygdala of smells with emotional components (e.g., alarm substances—the building is on fire!). The second is a region known as the "entorhinal cortex" (there is a small groove in the brain over the piriform cortex known as the "rhinal fissure". This region is at the end of it.). Entorhinal cortex is the gateway to a large region of the brain very involved in

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processing memories: the hippocampus. As such, the connection allows olfactory information to be stored as memories in many areas of the brain. Memory and olfaction are intimately connected; indeed a recent and interesting book by Wilson and Stevenson (2006, reviewed in *ChemoSense*, 2006, 8(3) p6 suggests that olfaction only functions well if memory processes are involved. In an older book, Harry Jerison (1973) suggested a longstanding evolutionary connection between memory and olfaction. As you may recall, mammals emerged from a class of small and relatively insignificant dinosaurs. Reptiles rely on their ears and eyes, and because they are not able to generate their own body temperatures are usually confined to being active in the day. The suggestion goes that the early protomammals became able to generate their own heat, and thus could become nocturnal and avoid predation by the larger, more successful dinosaurs. Vision is not as useful at night, so these animals evolved to depend on their olfactory systems. In order to use their olfaction, they needed to elaborate their ability to learn and remember space relations. For example, an animal tracking an odor source will sniff at two points and move towards the one with the strongest aroma. In order to do so, the animal needs to hold the odors and their relative locations in memory in order to compare them. It is indeed the case that olfaction is one of the crowning achievements of mammals, who have the largest and most elaborated olfactory anatomies. So much for olfaction being a "primitive" sense!

So we come to the end. Many details have be omitted here to provide a basic overview. To prove the point, both pars principalis of the AON and the piriform cortex have several different functional regions, there are small projections of the lateral olfactory tract that have not been mentioned, and since most areas of the brain project to several other areas, once you start travelling down circuits diagrams get more and more complex. We did not even mention the reciprocal or back projections between many areas, projections into the olfactory system from other brain regions, etc. Even this brief perusal, however, should be enough to convince you that the olfactory system is a complicated web of connections. It also points out that the topographic functioning that so clearly defines other sensory modalities is either lacking or as yet undiscovered in the higher olfactory pathways. However, one person's hopeless mess is another's intriguing problem. The olfactory circuits offer an opportunity for someone interested in general neurobiology, precisely because the organization appears to be different from those found in other systems, and thus may provide an alternate glimpse of brain function. So studying olfaction is important not only because it can help us understand the sense of smell, but also because it can help us understand novel and conserved principles about brain organization. But that is another story ■

REFERENCES AND SUGGESTED READING

Brunjes P.C., Illig, K.R. and Meyer E.A. 2005. A field guide to the anterior olfactory nucleus/cortex. *Brain Res. Reviews.* **50**:305-335.

DeMaria S, and Ngai J. 2010 The cell biology of smell. *J Cell Biol.* **191**:443-52.

Haberly, L.B. 2001. Parallel-distributed processing in olfactory cortex: new insights from morphological and physiological analysis of neuronal circuitry. *Chem Senses.* **26**:551-76.

Jerison, H. 1973. Evolution of the brain and intelligence. New York, Academic Press.

Kay L.M., and Sherman, S.M. An argument for an olfactory thalamus. 2007. *Trends Neurosci.* **30**:47-55

Porter J., Craven B., Khan R.M., Chang S.J., Kang I., Judkewitz B., Volpe J., Settles G., and Sobel N., 2007. Mechanisms of scent-tracking in humans. *Nat. Neurosci.* **10**:27-9.

Sakano, H. 2010. Neural map formation in the mouse olfactory system. *Neuron* **67**:530-542.

Shipley, M. T., and Ennis, M. 1996. Functional organization of olfactory system. *J. Neurobiol.* **30**:123-176.

Tirindelli, R, Dibattista, M., Pifferi, S., and Menini, A. 2009. From pheromones to -behavior. *Physiol. Rev.* **89:**921-956.

Wesson, D.W., and Wilson D.A. 2011. Sniffing out the contributions of the olfactory tubercle to the sense of smell: hedonics, sensory integration, and more? *Neurosci Biobehav Rev.* **35**:655-68.

Wilson, D. A., and Stevenson, R. J. 2006. Learning to smell: olfactory perception from neurobiology to behavior. Baltimore: Johns Hopkins University Press ■

NEWS

Sniffer helps in fight to recover $100Million NSW graffiti cost

Graffiti is now costing NSW communities and local governments $100 Million each year, say organisers of this year's Graffiti Action Day. This is money that comes directly from the pockets of ratepayers and property owners. It is money not being spent on better things.

Established in 1975, Keep Australia Beautiful NSW is a not for profit, environmental organisation that started Graffit Action Day with the help of the NSW Government as a way for local communities to take a very public and collective stand against illegal graffiti.

"It is well documented that an active approach to removing graffiti discourages further action by graffiti vandals, increases civic pride, can increase the value of an area and results in fewer local incidences of crime," Peter McLean, CEO of Keep Australia Beautiful NSW said.

New initiatives are being encouraged including planting trees, screening and designing the environment to prevent crime.

Several NSW councils are backing the technological solution offered by E-Nose Pty Ltd which sniffs the smell of spray paint and alerts authorities to graffiti vandal attacks while "in the act". In the latest version of the E-Nose (Mk4) the device interacts with CCTV to help verify the attack and to strengthen the evidence leading to conviction for graffiti crimes.

For more information: www.e-nose.info ■

13th Scientific Meeting of the Australasian Association for ChemoSensory Science (AACSS)

7-9 December 2011
Ascension Wine Estate, Matakana, New Zealand
(*one hour's drive north of Auckland*)

Save the Dates!

The 13th meeting of the AACSS will be held north of Auckland in wonderful Matakana close to wineries and beautiful beaches. The program will cover all aspects of chemosensory science in both invertebrate and mammalian systems. Please lock in those dates.

Please watch the AACSS website for more information including the programme, invited speakers, registration and abstract submission dates and details of accommodation: http://www.aacss.org/

Any queries regarding the meeting can be directed to Richard Newcomb,
Richard.Newcomb@plantandfood.co.nz

Upcoming Events

13-17 April 2011	**33rd AChemS** Tradewinds Resort, St Pete Beach Florida USA www.achems.org
3-5 May 2011	**ISOEN 2011** New York, USA www.olfactionsociety.org
6 June 2011	**Back to the Future: What's in the future for Sensory and Consumer Sciences?** Leatherhead Food Research, Surry, UK Registration: training@leatherheadfood.com
31 July to 2 August 2011	**20th International Clean Air and Environment Conference** CASANZ (change of date from 5-8 July) Auckland (Change of venue from Christchurch) New Zealand www.casanz.org.au
10-14 July 2011	**9th Pangborn Sensory Science Symposium** Bangkok, Thailand www.pangborn2011.com
24-29 July 2011	**Summer School on Human Olfaction** Dresden, Germany thummel@mail.zih.tu-dresden.de
12-16 November 2011	**Neuroscience 2011** Washington DC, USA www.sfn.org/am2011/
7-9 December 2011	**Australasian Association for ChemoSensory Science (AACSS)** Annual Scientific Meeting Matakana, Auckland, New Zealand www.aacss.org

ChemoSense (ISSN 1442-9098)
Web: chemosense.info
Published by **E-Nose Pty Ltd**
P.O. Box 488 Gladesville, NSW Australia 2111
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Production Team
Editor & Advertising: Graham Bell, g.bell@e-nose.info
Design and Layout: Lawton Design Pty Ltd

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