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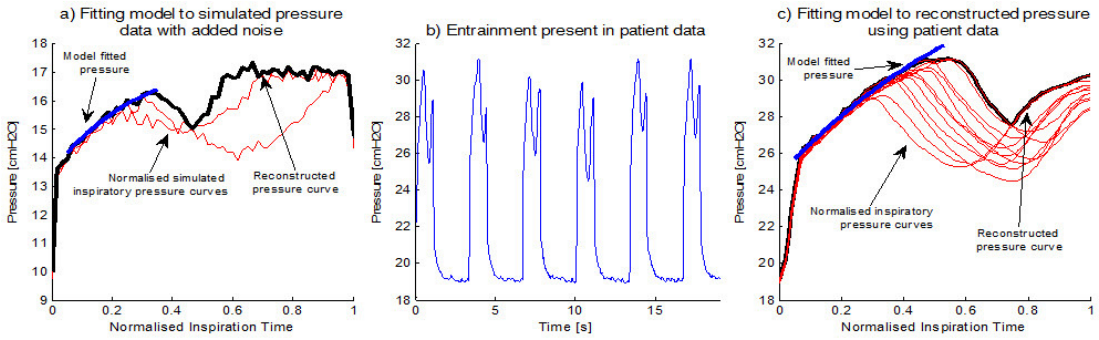
A Pressure Reconstruction Method to Estimate Respiratory Mechanics of Breathing Masked by Spontaneous Breathing Efforts, V Major[1], S Corbett[1], A Beatson[1], D Glassenbury[1], D Redmond[1], Á Szlávecz[2], B Andreu[1], S Davidson[1], NS Damanhuri[1], P Docherty[1], YS Chiew[1], C Pretty[1], G Shaw[3], JG Chase[1]; [1]Centre of Bioengineering, University of Canterbury, Christchurch, [2]Department of Control Engineering and Information Technology, Budapest University of Technology and Economics, Budapest, [3]Department of Intensive Care, Christchurch Hospital, Christchurch.

During fully controlled mechanical ventilation, patient-specific respiratory mechanics can be identified using mathematical models. However, spontaneous breathing (SB) efforts violate model assumptions and result in a loss of precision. This study investigates an iterative learning method to identify respiratory mechanics masked by SB entrainment.

A reconstruction method is proposed to enable model-based identification of underlying respiratory mechanics of breaths masked by SB entrainment. To validate this reconstruction method, it was tested on both simulated SB-entrained breaths and clinical data from a respiratory failure patient with SB entrainment during mechanical ventilation. The reconstruction method normalizes and combines several breathing cycles, resulting in a 'learned' data set with more information. This approach allows respiratory mechanics to be determined more accurately. The simulated airway pressure, patient airway pressure and pressure reconstruction method are shown in Figure 1.

Figure 1: Pressure Reconstruction Method for simulated data (a) and patient data (b &c)



To generate simulated breaths, a single compartment model is used to simulate the airway pressure and flow of a mechanically ventilated patient, with preset respiratory

elastance (25 cmH2O/l) and airway resistance (5 cmH2Os/l). A random sinusoidal waveform (f=1.6-10 Hz, amplitude 5-20% of peak pressure) is superimposed on the airway pressure data to simulate SB entrainment. These simulated breaths affect the model-based identification of respiratory elastance and resistance in the same way as real SB-entrained breaths, but the 'actual' underlying parameters are known.

The respiratory elastance and resistance calculated using the reconstruction method on simulated data were 24.6cmH2O/l, and 5.4cmH2Os/l (< 10% error). Application to patient data showed this method can provide more consistent identified elastance values and thus a better understanding of patient-specific respiratory mechanics without requiring muscle relaxants to paralyze the patient when identifying these values, thus reducing risk and invasiveness.

Association between telomere length and life stress in two New Zealand cohorts, S Jodczyk[1], JF Pearson[2], DM. Fergusson[3], LJ Horwood[3], JK Spittlehouse[3], PR Joyce[2], MB Hampton[1], MA Kennedy[1]; [1]Department of Pathology, [2]Department of the Dean, [3]Department of Psychological Medicine, University of Otago, Christchurch, New Zealand.

Telomeres are specialised structures that cap the ends of chromosomes and maintain the integrity of the genome. They shorten with each cell division, eventually reducing the telomere to a critical length and triggering cell senescence and apoptosis. Telomere length variability in the general population is thought to reflect lifetime exposure to environmental and biological stressors that impact on telomere maintenance. Previous research suggests that different stressors increase the rate of telomere shortening with potential impact on disease states and mortality later in life. Therefore, there is great interest in the application of telomere length measures as a biomarker of health or "biological age".

Average telomere length was measured in genomic DNA from human peripheral blood leukocytes using a quantitative polymerase chain reaction assay. The assay was applied to subjects from two longitudinal health studies, the Christchurch Health and Development Study (CHDS) (n=677), which has followed a birth cohort to age 35 years and the Christchurch Health, Aging and Lifestyle Cohort (CHALICE) (n=351), based on a population sample of 50 year olds.

We established and validated a modified method for accurately measuring telomere length. No associations were found between any biological or environmental stressor and telomere length for either cohort. The stressors examined in the CHDS cohort spanned each developmental domain and included birth weight, childhood maltreatment, substance use and misuse and life events. The correlations were very small ranging from -0.06 to 0.06, and none were statistically significant. The CHALICE cohort assessed biological stressors such as BMI and cholesterol levels and to measure general health status; the short form (SF36) health survey was used. All analyses led to the common conclusion that there was no evidence from these two cohorts that a wide range of life course stressors impacted on telomere length.

Deep brain stimulation of the nucleus accumbens attenuates relapse to cocaine seeking, Jennifer Hamilton[1], Jungah Lee J[1], Juan J. Canales[1]; Department of Psychology, University of Canterbury, Christchurch, New Zealand

Deep brain stimulation (DBS), a form of neurosurgical intervention that is used to modulate the electrophysiological activity of specific brain areas, has emerged as a form of therapy for severe cases of treatment-refractory addiction. Recent research suggests that the nucleus accumbens is a promising target area for DBS in addiction but optimal parameters of stimulation and long-term efficacy are yet to be established. Here, rats were implanted with a stimulating electrode in the right nucleus accumbens and exposed to chronic cocaine self-administration (0.5 mg/kg/infusion). Rats underwent drug seeking tests by exposing them to the self-administration context paired with cocaine challenge (5 mg/kg i.p.) on days 1, 15 and 30 after withdrawal from cocaine self-administration. Low-frequency (LF, 20 Hz) or high-frequency (HF, 160 Hz) DBS was applied for 30 min daily for 14 consecutive days starting one day after drug withdrawal. Rats exhibited robust drug-seeking 1, 15 and 30 days after withdrawal from cocaine self-administration, with responding being highest on day 15. Both LF and HF attenuated cocaine seeking on day 15 post-withdrawal by 36 and 48%, respectively. Both forms of stimulation were ineffective on the tests conducted on days 1 and 30. Neither LF nor HF DBS altered responding for infusions of cocaine or delivery of saccharin solution (0.1%). These data show that repeated unilateral DBS of the nucleus accumbens effectively attenuated cocaine relapse after 15 days of drug withdrawal, with therapeutic-like effects seemingly diminishing after DBS discontinuation. This evidence provides support for DBS as a promising intervention in intractable cases of stimulant addiction.

Magnetic Resonance Spectroscopy: a potential marker for cognitive impairment in Parkinson's disease, M Almuqbel[1,2], TR Melzer[1,2], D Myall[1,2], M MacAskill[1,2], L Livingston[1,2], T Pitcher[1,2], J Dalrymple-Alford[1,2,3] and T Anderson[1,2,4]; [1]Department of Medicine, University of Otago, Christchurch, New Zealand, [2]New Zealand Brain Research Institute, Christchurch, New Zealand, [3]Department of Psychology, University of Canterbury, New Zealand, [4]Department of Neurology, Christchurch Hospital, Christchurch, New Zealand

Parkinson's Disease (PD) affects 2% of those over 60. Beyond various motor symptoms, most patients develop cognitive impairment, and often dementia (PDD). Predictive biomarkers may be useful in future studies to prevent PDD. Our group has identified brain atrophy, loss of microstructure integrity and reduced perfusion in PDD with Magnetic Resonance Imaging (MRI). Magnetic Resonance Spectroscopy (MRS) was used here to identify brain metabolic changes associated with cognitive impairment and dementia in PD.

109 PD and 42 healthy participants completed neuropsychological testing. The patients were classified as either normal cognitive status (PDN, n=63), with mild cognitive impairment (PD-MCI, n=29), or with dementia (PDD, n=17). A $2\times2\times3cm^3$ MRS voxel was placed on the brain's posterior cingulate cortex (PCC) and four metabolites quantified: N-Acetylaspartate (NAA), Choline (Cho), Creatine (Cr), and myo-Inositol (mI). For each ratio (NAA/Cr, Cho/Cr, and mI/Cr), a separate

ANCOVA model assessed group differences with age, sex, years of education, and medication use as covariates. Pairwise comparisons were used to evaluate ratio differences across controls and individual PD groups.

Reduced NAA/Cr, relative to both PDN and controls, was found in PDD and likely reflects neuronal loss in advanced disease. Elevated Cho/Cr and mI/Cr was also evident in PDD and likely indicate gliosis. The intermediate and non-significant metabolic alterations in PD-MCI may suggest relatively preserved neuronal integrity; and therefore potential disease reversibility. MRS of the PCC may be a quantitative marker for cognitive impairment in PD and future anti-dementia therapy.

Rapid osseointegration of titanium scaffolds in a sheep model, S.J. Tredinnick[1,2,4], M.A. Woodruff[3], T.B.F. Woodfield[3,4], J.G. Chase[2]; [1]New Zealand ICT Innovation Institute (NZi3), University of Canterbury, New Zealand, [2]Department of Mechanical Engineering, University of Canterbury, New Zealand, [3]Biomaterials and Tissue Morphology Group, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Australia, [4]Christchurch Regenerative Medicine & Tissue Engineering Group, Department of Orthopaedic Surgery & Musculoskeletal Medicine, University of Otago, Christchurch, New Zealand

The osseointegration of three novel titanium scaffold materials, Cranial Mesh (CM) and Labrynth (L1 & L2), and a monolithic material, As Grown (AG), was evaluated for efficacy as orthopaedic biomaterials using a drill hole model in 12 sheep. All samples were manufactured by electron beam melting Ti6Al4V powder and shared a microsphere surface topography. A total of 120 cylindrical implants (Ø5mm x 6mm) were press fit in tibial defects in a distribution that mitigated location dependent healing. Scaffold materials had porosities and pore sizes that enabled rapid infiltration and long-term fixation in bone: L1 (73%, 660 μm), L2 (71%, 580 μm) and CM (65%, 480 μm).

Animals were sacrificed at 3, 6, and 12 weeks to investigate early fixation. Cortical bone samples were subjected to mechanical push-out testing and the peak stress and energy to failure (EtoF) measured (n=6). Cortico-cancellous bone samples were embedded in Technovit 9100 methacrylate resin and ground sections prepared (n=4). Midline sections (50 μm thickness) were stained with Goldner's trichrome, then imaged with an x5 objective. Regions of interest were standardized across all samples and blinded semi-automated histomorphometry was performed using OsteoMeasure (OsteoMetrics, Atlanta, USA). Tissue mineralization was compared with von Kossa and methylene blue – basic fuchsin stains.

Push-out stress increased with time for all samples up to maximum of 78% of that of the bone (L1, 12 weeks). Push out stress and EtoF was generally higher for L1 than L2 and CM, and for L1, L2, and CM vs. AG. Extensive direct bone to implant contact (BIC) was observed for the AG surface. Bone in-growth and BIC increased with time for all porous samples and newly formed bone completely infiltrated L1, L2 and CM at 12 weeks. These results show that all samples were able to strongly osseointegrate with the host tissue within 12 weeks.

Sequencing of pharyngeal pressure during wake and sleep swallowing, K Lamvik[1, 2], K Erfmann[2], R Jones[1,2], M-L Huckabee[1, 2]; [1]Communication Disorders, University of Canterbury, Christchurch, [2]Swallowing Rehabilitation Research Laboratory, New Zealand Brain Research Institute, Christchurch.

Recent clinical experience identified a patient cohort with an atypical swallowing impairment (dysphagia) characterized by mis-sequenced pharyngeal constriction, whereby patients are unable to coordinate streamlined bolus transfer from the pharynx to the oesophagus. This disruption in temporal sequencing has been suggested to be a maladaptive compensation to chronic dysphagia rather than a primary pathophysiologic feature. If true, we hypothesized that during sleep, with a reduction of supratentorial modulation, pharyngeal mis-sequencing seen in awake swallowing would return to a normal pattern.

Two male patients (33 and 46 years old, respectively) presented with severe pharyngeal mis-sequencing, with a separation of peak pressures in the upper and lower pharynx > 2 SD below the mean of 239 ms (95% CI, 215-263 ms). The latency of pharyngeal pressure generation was measured with discrete sensor pharyngeal manometry during sleep.

Immediately prior to the sleep study, the mean peak-to-peak latency of Patient 1 was 31 ms (95% CI, -71-133 ms), but this reverted to -58 ms (95% CI, -120-4 ms) when asleep. These outcomes were replicated in Patient 2, whose peak-to-peak latency regressed to -7 ms (95% CI, -83-97 ms) during sleep, from his pre-sleep latency of 93 ms (95% CI, 19-166 ms). Both patients reverted to a pattern of peak pressure in the lower pharynx occurring prior to peak pressure in the upper pharynx during sleep, consistent with their pre-treatment physiology. These case reports negate the role of maladaptive behaviour as a primary aetiology for pharyngeal mis-sequencing, and document the utility of comparing sleep to wake conditions to inform regarding parameters of cortical modulation of swallowing.

Skin Electroporation: Test Cell Re-Configuration, S Becker[1], D Collinson[1], E Mansell[1], J Robertson[1], A Hannon[1], B Zorec[2], N Pavselj[2]; [1]Department of Mechanical Engineering, University of Canterbury; [2]University of Ljubljana, Ljubljana, Slovenia

Skin electroporation involves the application of intense electric fields to in order to radically increase transdermal drug delivery across the skin's barrier layer, the stratum corneum (SC). A generally held view in the field of skin electroporation is that the skin's drop in resistance (to transport) is proportional to the number of pulses administered. Contrary to this belief, previous experiments by this group show that the application of high voltage pulses prior to the application of low voltage pulses act to decrease the total transport compared to the application of low voltage pulses alone. In order to further reconcile these unexpected experimental results with the underlying physics, the current group is redesigning the experimental Franz diffusion test cell specifically for the purposes studying such aspects of enhanced transport.

The transport of calcein (molecular charge: 4-) across dermatomed porcine skin was previously studied [2] in standard vertical glass Franz diffusion cells that are thermo

regulated at 37 °C by water circulation. A unipolar square wave pulse generator Cliniporator (Igea, Italy) was used for pulse delivery. The concentration of calcein was measured with spectrofluorometer (Jasco, FP-6300). The ability to perform experiment in the previous study, however was constrained by the configuration of the existing diffusion cells. The current project is instead using the experimental protocol as the criteria in order to design the geometry of the diffusion cells.

Theoretical investigations show that the increase in permeability to transport resulting from the large LTR evolution is hindered when the pre-existing SC has a high density of very small defects. Such defect size and distribution are attributed to the high intensity HV pulse. In order to better capture electroporation data, we use a diffusion cell that maximizes the ratio of aperture size to receiver volume that incorporates active enhancement technology into the test cell.

Trace amine-associated receptor 1 activation modulates methamphetamine's neurochemical and behavioural effects, Yue Pei[1], Rachel Cotter[1], Anja Harmeier[1], Damiana Leo[1], Raul R. Gainetdivov[1], Marius Hoener[1], Juan J. Canales[1]; Department of Psychology, University of Canterbury, New Zealand

Methamphetamine (METH) is currently a major source of public concern in New Zealand, but treatments for METH addiction are not yet available. The newly discovered trace amine-associated receptor 1 (TAAR1) has emerged as a promising target for treatment in stimulant addiction due to its ability to strongly regulate dopamine function. Here, we tested in rats the ability of RO5203648, a selective TAAR1 partial agonist, to modulate METH's physiological and behavioural effects. In experiment 1, RO5203468 dose- and time-dependently altered METH-induced locomotor activity, producing an early attenuation followed by a late potentiation of METH's stimulating effects. In experiment 2, rats received a 14-day treatment regimen during which RO5203648 was co-administered with METH. RO5203648 dose-dependently attenuated METH-stimulated hyperactivity with the effect becoming more pronounced as treatment progressed. After chronic exposure and 3-day withdrawal, rats were tested for locomotor sensitization. RO5203648 administration during the sensitizing phase prevented the development of METH sensitization. However, RO5203648, at the high dose, cross-sensitized with METH. In experiment 3, RO5203648 dose-dependently blocked METH self-administration without affecting operant responding maintained by sucrose, and exhibited lack of reinforcing efficacy on its own when tested as a substitute for METH. Neurochemical assays revealed that RO5203648 did not affect METH-mediated DA efflux and uptake inhibition in striatal synaptosomes. However, the results of in vivo microdialysis experiments showed that RO5203648 was able to acutely inhibit METH-induced accumulation of DA overflow in the nucleus accumbens. Taken together, these data highlight the significant potential of TAAR1 to modulate METH's neurochemical and behavioural effects, thus supporting the candidacy of TAAR1 as a therapeutic target for stimulant addiction.