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An exploration of mental health promotion in Aotearoa New Zealand: A qualitative study

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Mental health promotion focuses on promoting positive mental health for individuals, communities and populations. In recent years mental health has reappeared on the Aotearoa New Zealand (NZ) political agenda. However, the current level of knowledge and reporting about mental health promotion action occurring is limited. This study therefore aimed to explore what health promotion practitioners are currently doing to address mental health in Aotearoa NZ, in terms of both content and practice.

Between May and December 2019, semi-structured interviews were conducted with fifteen health promotion practitioners employed at various health organisations in Aotearoa NZ. Participants were selected using a combination of maximum variation and snowball sampling methods. Data were thematically analysed using both inductive and deductive methods.

Health promotion practitioners reported undertaking a diverse range of mental health promotion programmes/projects in Aotearoa NZ, including, but not limited to, programmes focused on: developing personal skills, creating supportive environments, encouraging community action and activating messages from national initiatives at a local level. Participants reported undertaking a variety of processes and utilising various approaches in the planning and evaluation of their programmes/projects, for example needs assessment, equity and Treaty-based practice, collaboration and process evaluation. However, various factors, operating at the systems level, restricted them from being able to undertake "best practice" mental health promotion. In particular, participants reported operating within short-term and prescriptive contractual agreements, a tertiary-focused healthcare system, a fragmented field and a limited workforce, which created significant challenges for their mental health promotion practice.

This study highlights a number of potential opportunities for future mental health promotion action and practice in Aotearoa NZ. Findings highlight a critical need for system level action to create an environment that encourages and supports health promotion practitioners to undertake best practice mental health promotion in Aotearoa NZ.

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Vaccination, vaccine hesitancy and COVID-19 in New Zealand, 2018–2021.

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Vaccine hesitancy is considered a serious threat to public health, due to worldwide decline in vaccine uptake and resurgence of vaccine preventable diseases. With mass vaccination underway for coronavirus disease 2019 (COVID-19), opposition and reluctance could hinder success and therefore must be understood and addressed. This research aimed to understand attitudes towards vaccination and drivers of hesitancy within a New Zealand context from 2018 to today, with particular emphasis on the COVID-19 vaccine.

Literature searches were conducted in November 2020 and June 2021, to gather both historical and current research on vaccination attitudes in New Zealand and factors influencing vaccine hesitancy. Key words included coronavirus, vaccine hesitancy, vaccination, anti-vaccination, infodemic, misinformation and social media. Online and unpublished sources were also used, along with the *Otago Daily Times* (March 2020–February 2021) to provide a local perspective amidst a global pandemic.

Drivers of attitudes and vaccination hesitancy are multifacto-

rial. With social media now so prevalent, misinformation and the "anti-vax" sentiment can reach more people than ever before. The speed at which the COVID-19 vaccine was developed and approved for use has fuelled hesitancy, with safety appearing the predominant concern. Vaccine hesitancy can be overcome by actively addressing and correcting misinformation with scientifically backed messaging, that is tailored to local communities. Government and regulatory bodies must communicate transparently to the public to avoid confusion and overcome reluctance. Healthcare professionals also play an important role in fostering trust in vaccines within the communities they work in, but they must be well supported by the wider healthcare system.

Vaccine hesitancy is a clear threat to a successful vaccination campaign for COVID-19. Misinformation circulating both online and in person can influence decision-making surrounding vaccination. Hesitancy must be actively and publicly addressed in order to increase vaccine uptake.

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Replication of a Māori and Pacific-specific T2D-risk variant within *JAZF1*

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Māori and Pacific individuals have a two times greater risk of Type II diabetes (T2D) compared to other population groups in New Zealand. This provides a unique opportunity to explore the hypothesis that some of this risk is attributed to genetic variation. Genome sequencing of 56 Māori and Pacific individuals led to the identification of a Māori- and Pacific-specific non-coding variant, *rs150587514*, in the first intron of the *JAZF1* gene. This variant is common in Māori and Pacific people (minor allele frequency (MAF) of >10%) but uncommon in other population groups (MAF <0.1%). *JAZF1* is a gene essential for β-cell function and insulin secretion. Previous unpublished work in 1,821 Māori and Pacific individuals found that the C risk allele conferred a 1.6-fold greater risk of developing T2D compared to those without the risk allele (OR = 1.63 [95% CI 1.27; 2.15], $p = 3.9 \times 10^{-4}$). The aim of the current work was to validate this association by genotyping an independent cohort of Māori and Pacific individuals to test the replicability of this previously identified association. An independent Māori and Pacific cohort were recruited through a partnership with the Ngāti Porou Hauora Charitable Trust. This resulted in a replication cohort of 478 Māori and Pacific participants. These individuals were genotyped using custom designed Taqman probes in a Taqman genotyping assay. Using these genotypes and corresponding phenotypic data, a logistic regression association analysis was conducted between *rs150587514* and T2D, with T2D as the outcome variable. The association between *rs150587514* and T2D risk was replicated, and the direction of effect remained consistent with the original analysis (OR = 2.07 [95% CI 1.27; 3.37], $p = 3.5 \times 10^{-3}$). Importantly, in combination with the original data, the association between *rs150587514* and T2D was strengthened (OR = 1.73 [95% CI 1.36; 2.19], $p = 6.2 \times 10^{-6}$). The meta-analysis of these two cohorts indicates that per *rs150587514* C-risk allele, Māori and Pacific individuals have a 1.7-fold greater risk of developing T2D. This is the first validated Māori- and Pacific-specific variant associated with an increased risk of T2D. This finding adds to our understanding of the genetic contribution to complex disease and has a potential long-term impact in precision medicine initiatives directed to Māori and Pacific communities, working to decrease the health inequities that exist in Aotearoa.

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Infra-slow pink noise stimulation can increase default-mode network activity in individuals with early Alzheimer's disease

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Alzheimer's disease (AD), the most common form of dementia, is a significant and growing health challenge worldwide. Current available treatments for AD have poor efficacy. Decreased activity within default-mode network (DMN) has been demonstrated as a potential biomarker for tracking AD progression and is a recommended target for brain stimulation. This pilot study explored a novel high-definition transcranial infra-slow pink noise stimulation (HD-tIPNS) technique for increasing DMN activity in individuals with early AD.

The study was a double-blinded (participant and assessor) pilot randomised placebo-controlled parallel trial with two intervention arms. For treatment group (n = 9), HD-tIPNS targeting hubs of DMN [posterior cingulate cortex (PCC), pregenual anterior cingulate cortex (pgACC), left and right parahippocampal gyrus (LPHG and RPHG)] was delivered for a single session of 30 minutes. For sham group (n = 7), stimulation was applied for two minutes at the beginning and end of the session. Electroencephalographical data were collected at baseline and immediately post-intervention. Standardized low-resolution brain electromagnetic tomography (sLORETA) was used to compute and compare current density (CD) at the PCC, pgACC, LPHG and RPHG for the infra-slow (0.01–0.1 Hz),

slow (0.2–1.5), delta (2–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10.5–12 Hz), beta1 (12.5–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz) and gamma (30.5–44 Hz) bands.

When compared to sham group, the treatment group demonstrated increased CD in the PCC [slow (p = 0.0411) and gamma (p = 0.0315) bands], LPHG [slow (p = 0.0111), beta2 (p = 0.0454) and beta3 (p = 0.0195) bands], and RPHG [slow (p = 0.0222), beta2 (p = 0.0317), beta3 (p = 0.0132) and gamma (p = 0.0136) bands].

These preliminary findings showed that a single-session of HD-tIPNS is capable of increasing DMN activity in individuals with early AD. Future research could evaluate the efficacy of multi-session HD-tIPNS for improving cognition in individuals with early AD.

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Agmatine attenuates actin dynamic alteration and synaptic dysfunction in aged rats

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Cytoskeletal protein actin forms the morpho-functional platform at synapses (the communication points between neurons) and changes dynamically between monomeric globular (G-actin) and polymerised filamentous (F-actin) forms in response to neuronal activity. Such actin dynamics is essential for almost all aspects of synaptic physiology, including long-term potentiation (LTP). Synaptic dysfunction contributes to age-related cognitive decline, and agmatine supplementation attenuates memory deficits in aged rats. However, little is known how agmatine affects synaptic function. This study investigated the effects of long-term agmatine supplementation on cytoskeletal protein actin and synaptic function in aged rats.

The parahippocampal region was dissected from female Sprague-Dawley rats at 18 months of age following daily agmatine (agm) supplementation (50 mg/kg) via food chow for 14 weeks (aged-agm, n = 10), and rats at 4 months (young, n = 7) and 18 months (aged, n = 8) provided with normal food chow. Synaptosomes enriched with synaptic nerve terminals were prepared for the measurements of F- and G-actin via western blot and chemically induced LTP (cLTP) via a radioactive assay.

One-way analysis of variance revealed a significant difference between groups in the F-/G-actin ratio ($F_{2,18}$ = 13.39, P = 0.0003), with a reduced F-/G-actin ratio in the aged group relative to the young group (P < 0.001). Agmatine supplementation significantly increased the F-/G-actin ratio when the aged-agm and aged groups were compared (P < 0.05). Moreover, there was also a significant difference between groups in cLTP ($F_{2,19}$ = 6.27, P = 0.008), with reduced cLTP in the aged group when compared to the young group (P < 0.05) and aged-agm group (P < 0.01).

These findings demonstrate that agmatine supplementation significantly attenuated age-related alteration in actin dynamics and normalised cLTP deficits in aged rats, which underlie the anti-aging and memory enhancing effects of agmatine. Future research will explore the potential of agmatine in maintaining healthy brain aging.

Estrogen receptor alpha activation stimulates the Coolidge effect but has no effect on the sexual refractory period of estrogen-deprived male rats

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Estrogen is involved in normal male sexual function and can exert its effects on cells by activating estrogen receptors (ERs) such as ERa and ERb. Here, we explored the role of ERa activation on the sexual refractory period (ie, the time when males cannot be sexually aroused after an ejaculation) and the Coolidge effect (ie, the shortening of the refractory period when a novel sexual partner is introduced after ejaculation). We investigated the effects of ERa administration on different parameters of sexual behaviours including mounting, intromission, and ejaculation in estrogen-deprived male rats.

Twenty-four sexually experienced male rats (8 per group) were treated for 29 days with: (1) saline (Control group), (2) aromatase-inhibitor (Fadrozole, 1 mg/kg) or (3) aromatase inhibitor daily with the addition of ERa agonist on the last day (ERa group, propyl pyrazole triol, 1 mg/kg). On day 29, all groups had a mating test with one female until reaching sexual satiety (30 minutes without ejaculation), and then exposed to a different female until a second sexual satiety.

On day 29, the Fadrozole group had similar mounting (3.0 ± 2.3) and intromission (18.0 ± 12.2) frequencies than the Control group. However, significantly lower ejaculation (1.3 ± 1.0) frequency and longer refractory period (725.9 ± 266.2 s) compared to the Control group (p < 0.001 for all) was observed. The ERa group had significantly higher mounting frequency (16.6 ± 8.0) than the other groups (p < 0.01 vs. Control, p < 0.001 vs. Fadrozole) but had similar time to reach sexual satiety, intromission frequency and ejaculation frequency as the Fadrozole group.

Following introduction of the second female, the Fadrozole group had similar mounting and intromission frequencies but lower ejaculation frequency (p < 0.05) than the Control group. The ERa group, however, had higher mounting frequency (5.9 ± 2.0) than the Fadrozole group (p < 0.05).

In conclusion, estrogen plays a role in controlling the sexual refractory period and the Coolidge effect. Specifically, estrogen regulates the Coolidge effect through ERa activation.

This study will provide further pre-clinical evidence on the role of estrogen in male sexual function, which will be relevant to males who face estrogen deprivation.

Evaluation of vascular endothelial growth factor-A_{165} glycoforms in angiogenic assays

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Vascular endothelial growth factor-A_{165} (VEGF-A_{165}) is the key mediator of angiogenesis which has been explored as a therapeutic agent to control angiogenesis and revascularisation of ischaemic tissues. Unfortunately, the use of VEGF-A_{165} has failed to improve angiogenic outcomes in clinical trials, despite showing promising results in vitro and in vivo. We propose that these failures occurred due to therapies using VEGF-A_{165} lacking appropriate glycosylation. The aim of this project was to test the angiogenic capacity of differentially glycosylated isoforms (glycoforms) of VEGF-A_{165}.

Chemically synthesised (unglycosylated), *Escherichia coli*-produced (unglycosylated) and human embryonic kidney (HEK)293 cell-produced (glycosylated) forms of recombinant human VEGF-A_{165} were evaluated in *in vitro* angiogenic assays. A Ba/F3 bioassay was employed to quantify cell proliferation upon VEGF receptor (VEGFR)-2 binding at varying doses of VEGF-A_{165} glycoforms. A Matrigel® assay was utilised to assess endothelial cell tube formation at varying doses of VEGF-A_{165} glycoforms. A barrier assay was used to measure Evans blue-conjugated BSA leakage through an endothelial cell monolayer in response to 25 ng/mL of each VEGF-A_{165} glycoform. Three replicates were conducted for each assay.

VEGFR-2 receptor binding of the VEGF-A_{165} glycoforms induced similar dose-dependent upregulation of cell proliferation, increasing E_{max} by 2.37 to 3.54-fold compared to control. All VEGF-A_{165} glycoforms did not produce a dose-response curve for parameters of endothelial tube formation evaluating cell migration. All VEGF-A_{165} glycoforms at 25 ng/mL induced a 2.79- to 3.24-fold increase in leakage compared to assay control on the endothelial cell monolayer. No significant differences were detected between VEGF-A_{165} glycoforms in any assay (Brown-Forsythe and Welch ANOVA).

These findings show that the chemically synthesised VEGF-A_{165} is biologically active and suggests that glycosylation may modulate the angiogenic capacity of VEGF-A_{165}. However, further studies are needed to determine if the VEGF-A_{165} glycoforms exhibit differences in pharmacokinetics that may impact their utility as treatments for vascular diseases.

Dissecting the receptor signalling events responsible for the immune suppressive and immune stimulatory effects of IL-10

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Interleukin 10 (IL-10) is a dynamic cytokine produced by most adaptive and innate immune cells. Although IL-10 is known as a potent anti-inflammatory cytokine, it can also stimulate the activity of B cells, cytotoxic T cells, natural killer cells and mast cells. This has hindered the use of IL-10 as a therapeutic in immune mediated diseases. This project aimed to identify IL-10 mutants that exhibit signalling bias to develop as selective anti-inflammatory therapies. We hypothesised that structurally guided human IL-10 mutants with altered receptor affinity could bias IL-10 signalling towards therapeutic immune suppressive pathways.

Peripheral blood mononuclear cells (PBMC) derived from two healthy donors were stimulated with wild-type human (h)IL-10 or receptor-selective mutant IL-10s. PBMC were stained for cell surface markers such as CD14 as well as intracellular phosphorylated (p) proteins pAKT1 and pSTAT3. Phospho-flow cytometry was used to detect phosphorylated proteins in specific cells, with changes in the geometric mean fluorescence intensity (gMFI) measured.

Stimulation of CD14+ monocytes with hIL-10 induced a mean (± SEM) pSTAT3 gMFI of 324 ± 37. Similarly, the IL-10 mutants induced mean gMFIs ranging from 307-331 ± 12-3. However, the IL-10 mutants displayed differential pAKT1 activation in CD14+ monocytes with mean gMFIs of 1,317-1,456 ± 2-21 which was substantially reduced compared to that induced by hIL-10 with a gMFI of 2,427 ± 271.

The differential pAKT1 gMFI with retention of pSTAT3 between the mutants and hIL-10 suggests that though changes to receptor affinity may not affect the JAK-STAT3 pathway, PI3K-AKT1 signalling could be subject to manipulation. This could provide a mechanism of decoupling the immune stimulatory and immune suppressive activity of IL-10 which would contribute to improved IL-10 therapies for immune mediated disease.

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