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TWIN-10: protocol for a 10-year longitudinal twin study of the neuroscience of mental well-being and resilience

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ABSTRACT

Introduction Mental well-being is a core component of mental health, and resilience is a key process of positive adaptive recovery following adversity. However, we lack an understanding of the neural mechanisms that contribute to individual variation in the trajectories of well-being and resilience relative to risk. Genetic and/or environmental factors may also modulate these mechanisms. The aim of the TWIN-10 Study is to characterise the trajectories of well-being and resilience over 12 years across four timepoints (baseline, 1 year, 10 years, 12 years) in 1669 Australian adult twins of European ancestry (to account for genetic stratification effects). To this end, we integrate data across genetics, environment, psychological self-report, neurocognitive performance and brain function measures of well-being and resilience.

Methods and analysis Twins who took part in the baseline TWIN-E Study will be invited back to participate in the TWIN-10 Study, at 10-year and 12-year follow-up timepoints. Participants will complete an online battery of psychological self-reports, computerised behavioural assessments of neurocognitive functions and MRI testing of the brain structure and function during resting and task-evoked scans. These measures will be used as predictors of the risk versus resilience trajectory groups defined by their changing levels of well-being and illness symptoms over time as a function of trauma exposure. Structural equation models will be used to examine the association between the predictors and trajectory groups of resilience and risk over time. Univariate and multivariate twin modelling will be used to determine heritability of the measures, as well as the shared versus unique genetic and environmental contributions.

Ethics and dissemination This study involves human participants. This study was approved by the University of New South Wales Human Research Ethics Committee (HC180403) and the Scientific Management Panel of Neuroscience Research Australia Imaging (CX2019-05). Results will be disseminated through publications and presentations to the public and the academic community. Participants gave informed consent to participate in the study before taking part.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The TWIN-10 longitudinal twin study will identify resilience versus risk trajectories of mental health and mental illness over 12 years, with multimodal assessments undertaken at four timepoints.
⇒ Resilience trajectories will map individuals who increase or maintain mental well-being despite exposure to psychological trauma, whereas risk trajectories will map individuals who have reduced levels of well-being following trauma exposure, each relative to individuals who report no trauma exposure.
⇒ Our twin design provides the opportunity to explicitly disentangle the contributions of genetic and environmental factors on risk and resilience trajectories characterised by psychological scales, general and cognitive emotional function and neuroimaging data of brain function.
⇒ A key challenge will be the retention of participants across each timepoint over the life of the study.
⇒ Because the study focuses on a national twin sample of European ancestry to minimise genetic stratification effects, generalisations of the study outcomes may be specific to Caucasian adults.

INTRODUCTION

While it is now widely accepted that mental health is more than the mere absence of mental illness, there is still a large gap in understanding the neural and behavioural mechanisms that contribute to optimal mental well-being. Well-being consists of two subcomponents: subjective well-being, which relates to happiness and life satisfaction[1]; and psychological well-being, which comprises the human attributes that underpin a sense of meaningful life purpose, such as mastery, autonomy and setting goals.[2] It has been shown that both components uniquely contribute to total (or composite) well-being, and achieving a flourishing state of well-being requires high levels of both.[3 4] Previous studies have shown associations between high well-being and improved quality of life and happiness,[5] healthy ageing and increased lifespan,[6] as well as decreased risk for illness

and death,[7] indicating the importance of identifying the underlying factors that promote mental well-being. Yet, mental health research has mostly targeted identifying factors and biomarkers that contribute to risk for psychopathology, such as anxiety and depression, rather than those that contribute to optimal psychological functioning, highlighting the need for further studies that focus on maximising well-being and developing resilience in the face of adversity.

Resilience is defined as a dynamic process encompassing both a swift recovery from adversity and trauma and the ability to maintain optimal levels of well-being after exposure.[8] In light of recent events, such as the global pandemic, fostering resiliency to adverse events has become particularly pertinent. However, there is still a significant gap in knowledge regarding the possible psychological and neurobiological mechanisms that underlie mental well-being and resilience. In terms of well-being, functional magnetic resonance imaging (fMRI) studies have started to identify regions of interest including increased functional activity in the amygdala, striatum, ventral anterior cingulate cortex, dorsolateral prefrontal cortex (PFC) and parietotemporal regions in response to emotionally salient information,[9–12] as well as between well-being measures and resting-state fMRI metrics such as regional homogeneity[13 14] and functional connectivity.[15 16] In terms of resilience, previous neuroimaging studies have reported structural changes in the amygdala, anterior cingulate cortex, PFC and the hippocampus as possible markers,[17] while fMRI outcomes implicate activation differences in regions such as the ventral PFC, insula and the anterior cingulate cortex that are involved in emotion regulation and attentional control,[18 19] and dynamic connectivity changes within the default mode network during a cognitive oddball task as a function of trait resilience.[20] Interestingly, neural circuits that underlie emotion functioning show some overlap between mental illness (eg, anxiety and depression) and well-being. For example, fMRI studies in clinical patients show decreased PFC activation during emotion regulation, as well as increased activation in the amygdala in response to fearful stimuli,[21] while in resilient individuals, the opposite pattern has been reported (ie, increased PFC during regulation and decreased/inhibited amygdala in response to aversive stimuli).[22 23] However, despite a wealth of clinical studies examining underlying circuits subserving other cognitive processes such as executive function and reward processing in patients, similar research lines in resilient individuals are only starting to develop.

There is also a lack of synthesis thus far on the neural signatures of well-being and resilience in existing studies, largely driven by the substantial heterogeneity in defining the two constructs. Studies examining well-being often focus on either subjective or psychological well-being, despite theoretical frameworks suggesting that both contribute to overall mental health, and a composite measure is a better indicator of optimal psychological functioning.[4] Research on resilience operationalise the construct usually in one of three ways: (1) as the absence of psychopathology following trauma or adversity; (2) as a personality trait (eg, self-esteem and positive affect); or (3) as a dynamic process by which an individual positively adapts to an environment in the face of adversity.[24] The variation in studies using disparate definitions has hampered the integration of findings across populations, experimental paradigms (eg, task vs resting state) and research modalities (eg, behavioural vs neuroimaging). In particular, resilience studies often use targeted populations, such as military cohorts and firefighters, and/or those who do not develop post-traumatic stress disorder after trauma,[25–28] which especially limit the generalisability of their findings.

Within the context of neural correlates, changes in the brain that are related to well-being and resilience are unlikely to happen in isolation. In other words, the association between neural networks, mental well-being and resilience is likely to impact the dynamic interactions between genetic and environmental influences, whereby heritable factors affecting brain structure and function are likely to form the bases on which environmental effects unfold over time to determine the level of resilience. By using a twin design, we are able to establish the genetic features from those that result from exposure to life events (environment). As monozygotic (MZ) twins share 100% of their genes compared to dizygotic (DZ) twins with 50% shared genetics, we can deduce increased similarity in MZ twins to have a heritable basis, while increased similarity in DZ twins may be attributed to shared environment (eg, parenting style, education). Using a multivariate modelling approach, we can deduce the variations in these gene–environment effects on risk versus resilience, and how they modulate neural structure and function. Previous studies have shown that genetics and environment play a role in well-being and resilience with heritability estimates ranging from 36% to 48% for well-being[3 5] and from 35% to 64% for resilience.[29] This suggests that environmental factors also play a large role in determining one's level of well-being and resilience, spanning adverse effects (eg, a stress response from trauma) to protective buffers (eg, secure and caring parenting, enriching environment).[8] However, the potential moderating effects of such factors have not yet been examined in the context of risk versus resilience, and how they determine individual differences.

Understanding the processes by which individuals develop resilience during their lifespan requires longitudinal data that allow tracking of one's mental health trajectory over a time period. Most of the current literature focuses on cross-sectional results of resilience, due to time and budget constraints associated with longitudinal data collection. Although such studies provide valuable insight into the associations between variables of interest, there is an inherent inability to derive resilient profiles as this requires ongoing observations of response to adversity over time as well as the directional impact on neural

mechanisms, which can be addressed by adopting a longitudinal design. By observing risk and resilient profile trajectories over time in a sample of participants who were all healthy at baseline, and with no history of psychiatric illness, we can identify the unique neural and behavioural markers that correspond to these trajectories, and build a novel multidimensional profile of risk and resilience.

The purpose of the current TWIN-10 Study is to identify the resilience versus risk neural profiles of mental health and illness in an adult twin sample over a 10-year and 12-year period (times 3 and 4). This is a cohort study, following up 1669 healthy twins previously tested between 2009 and 2012 at baseline (time 1) and then again at 1-year follow-up (time 2) between 2010 and 2013 (the TWIN-E sample[30]). From the TWIN-E Study, we were able to create the COMPAS-W Wellbeing Scale.[3] This 26-item scale measures composite (ie, both subjective and psychological) well-being as well as six subcomponents that include Composure, Own-worth, Mastery, Positivity, Achievement, and Satisfaction. This scale has shown strong internal reliability, test–retest reliability over 12 months, and construct validity with other health-related indicators in adults aged 18–61 years.[3] It has also been validated for use in adolescents aged 12–16 years, and across four countries including Australia, Canada, China and New Zealand.[31] Using this scale, we have established several unique biomarkers that correlate with well-being at baseline. For instance, in terms of psychological and physical health indicators, we have shown that higher well-being is associated with low depression and anxiety scores,[32] as well as higher levels of sleep and exercise, increased intake of fruit/vegetables and better work performance,[3] and more approach-focused forms of coping strategies.[33] In terms of cognitive functioning, we found associations between higher well-being and superior cognitive functioning related to sustained attention, inhibition, cognitive flexibility and working memory, while depression and anxiety symptoms were negatively associated with cognitive functioning.[34] We also observed faster behavioural response times to happy faces in individuals with high well-being, while those with higher depression and anxiety symptoms displayed slower reaction times.[35] On a neural level, we reported associations between higher well-being and an electroencephalography (EEG) resting-state profile of high alpha and delta and low beta (ABD) power,[36] a reduced pons grey matter volume localised to the locus coeruleus,[37] increased fMRI activity in the right inferior frontal gyrus in response to happy faces during an emotional faces task,[38] and decreased insula activation during a sustained attention continuous performance task.[39] Finally, in terms of genetics, we confirmed a polygenic score of well-being to be predictive of COMPAS-W scores, and derived nine subthreshold candidate genes from a genome-wide association study analysis of the COMPAS-W scores.[40]

As our sample consisted of twin participants, we used twin modelling methods to determine heritability estimates of: (1) total COMPAS-W well-being (48%, with h^2 ranging from 24% to 43% for the six subscales[3]); (2) cognitive and emotional functioning (ranging from 19% to 55% for cognitive processes and from 23% to 37% for emotion processes[34 35]); (3) EEG frequency bands (ranging from 54% to 91% for the alpha, beta, theta and delta bands, and 37% for the ABD interaction[36]); (4) pons structural volume (at 20%[37]); and (5) fMRI activation (20% in the inferior frontal gyrus in response to happy emotional faces, and 15%–18% in bilateral insula during sustained attention[38 39]). Finally, using multivariate twin modelling, we have been able to confirm the role of shared genetics and environmental factors in each of the phenotypic associations. For instance, we found evidence to suggest that the links between well-being and variables including EEG resting state (ABD interaction[36]) depression and anxiety symptoms[32] and cognitive inhibition[34] were mostly genetically driven, whereas the links between well-being and variables including emotion-related neural activity[38] and pons volume[37] were mostly environmentally driven. Together, these results identify for the first time how genetics versus life experience can modulate the links between neural markers and well-being. However, as all of these associations were determined at baseline, the relative direction of influence cannot be ascertained. With longitudinal data, we will be able to more clearly delineate how changes in biomarkers at one timepoint influence well-being at later timepoints (and vice versa), and how our genetics and environmental exposures including stress, trauma and positive life experiences may modulate these pathways over time.

The TWIN-10 longitudinal study of mental well-being and resilience is a continuation of TWIN-E, and aims to evaluate long-term changes in neurocognitive, neuroimaging and psychosocial factors, and their impact on well-being and resilience over the 10–12-year period. The aims of the current study are threefold[1]: to categorise individuals showing risk versus resilient profiles in terms of non-linear changes in mental health outcomes in response to adversity over time[2]; to track the longitudinal changes in neurocognitive performance, and the structural and functional changes in the brain using MRI that correspond to these trajectory profiles[3]; and to unravel the relative contribution of genetics and environmental factors in modulating these shared neurocognitive and neural networks supporting risk versus resilience using twin design models (MZ vs DZ).

Methods and analysis

Participants

Participant recruitment was conducted by Twins Research Australia (TRA), which is an Australian national register of twin volunteers interested in participating in research studies. TRA was responsible for recruiting the initial TWIN-E sample of twins, which resulted in 1669 twins completing at least one component of the original study. Inclusion criteria for the original TWIN-E Study in 2009 included being a twin (either MZ or DZ), aged between 18 and 65 years, having English as primary language, and

being of European ancestry (in order to avoid population stratification effects in genetic analyses). Exclusion criteria consisted of either currently having or having a history of psychiatric/neurological/genetic disorders, brain injury, other medical conditions (eg, cancer, heart disease, hepatitis), substance abuse (eg, drug, alcohol) and sensory impairments (eg, hearing, hand movement, vision).

For the current TWIN-10 Study, the start and planned end dates are June 2019 and December 2023. TRA approached the initial 1669 participants who completed time 1 measurements for TWIN-E. From this approach, we received contact details for 920 participants who agreed to participate in TWIN-10. This included 173 participants who were eligible for the MRI component. Online data collection for time 3 (June 2019 to December 2020) resulted in 517 participants completing all three sections of the component (Qualtrics, WebNeuro and Cambridge Neuropsychological Test Automated Battery (CANTAB)) and a further 86 participants who completed at least one of the sections (n=603). Out of the 173 participants invited for the MRI component, 121 agreed to participate, which began in March 2020 and is still ongoing with delays due to COVID-19. Time 4 of TWIN-10 started in August 2021, which is a 2-year follow-up of time 3, and consists of inviting time 3 participants to again return to complete an online testing component consisting of questionnaires and WebNeuro. Only those who completed at least one section of the time 3 online component are invited back for time 4 (target n=603).

Study design

TWIN-10 is a longitudinal follow-up study of the TWIN-E cohort, which began 10 years prior in 2009 as a multisite study of 1669 healthy same sex 18–65 year-old MZ and DZ Australian twins. TWIN-E included two timepoints, baseline (time 1) and a 1-year follow-up (time 2).[30] Briefly, time 1 consisted of three separate components conducted between 2009 and 2012: (a) an online assessment of psychological measures and neurocognitive tasks delivered via WebQ and WebNeuro completed remotely and across Australia as well as collection of saliva samples for DNA genotyping (n=1669); (b) an EEG session in Sydney and Adelaide labs, which included EEG measurements during resting state, followed by event-related potential recordings during six emotion and cognitive tasks (n=441); and (c) an MRI session in the Sydney Westmead lab, which consisted of four tasks, a structural scan, a diffusion-weighted scan, and a proton density scan (n=270). Time 2 was the longitudinal component of TWIN-E, and consisted of repeating the WebQ and WebNeuro online measures 12 months after their initial completion. This took place between 2010 and 2013. Of the 1669 participants who completed baseline, 1347 participants completed the time 2 measures (ie, 81% retention). Time 2 also consisted of a separate optional randomised control trial of cognitive brain training for a subset of participants (n=352) who had completed both times 1 and 2 measurements, which took place between 2010 and 2013.[41]

Recruitment and data collection for TWIN-10 began in 2019. It consists of two further timepoints of data collection which includes online psychological and neurocognitive tasks, and MRI subset components (time 3), and a 2-year online-only follow-up (time 4). Time 3 includes two separate components: (a) an online testing component, including psychological measures presented via Qualtrics and two sets of neurocognitive tasks using WebNeuro and CANTAB test batteries and (b) an MRI component, consisting of five functional tasks, a resting state scan and a diffusion-weighted scan. Recruitment by TRA began in June 2019, targeting the 1669 participants who completed at least the time 1 online component (TWIN-E). A subsample of 270 participants who completed the MRI at time 1 were further invited to participate in the MRI session for TWIN-10. Data collection for the online component took place between June 2019 and December 2020. MRI testing began in March 2020 and remains to be completed in late 2022, accounting for multiple pauses in testing due to COVID-19. For time 4, those who have completed at least the online component at time 3 will be invited back for another online component follow-up, which will consist of questionnaires via Qualtrics, and neurocognitive tasks via WebNeuro only. This begun in the second half of 2021 and will extend into the end of 2023 for completion. In total, this will result in the collection of psychometric measures and neurocognitive task data for four timepoints (times 1 and 2 during TWIN-E, and times 3 and 4 during TWIN-10; figure 1).

Measurements and procedures

Questionnaire and neurocognitive assessments (times 3 and 4)

For the online testing component of time 3, participants were required to complete a set of self-report questionnaires on Qualtrics, as well as two sets of neurocognitive tasks (WebNeuro and CANTAB) on their own personal computers. Personalised links to access all three parts were sent to each participant individually to ensure that the data saved from each link was for that particular participant. In total, this component took around 1.5–2.5 hours to complete, with instructions to take short breaks between each part. Online assessments will be repeated at time 4, which will include a subset of questionnaires used at time 3 (table 1) as well as the WebNeuro neurocognitive tasks (table 2). Overall, being a longitudinal study, some of the questionnaires and neurocognitive assessments were repeated across all sessions as they were critical to well-being and resilience measurement, others were only collected at time 1 as they did not require repeating (eg, childhood trauma and parenting style) and some new measures were added to times 3 and 4 in order to explore new potential correlates of well-being that were not

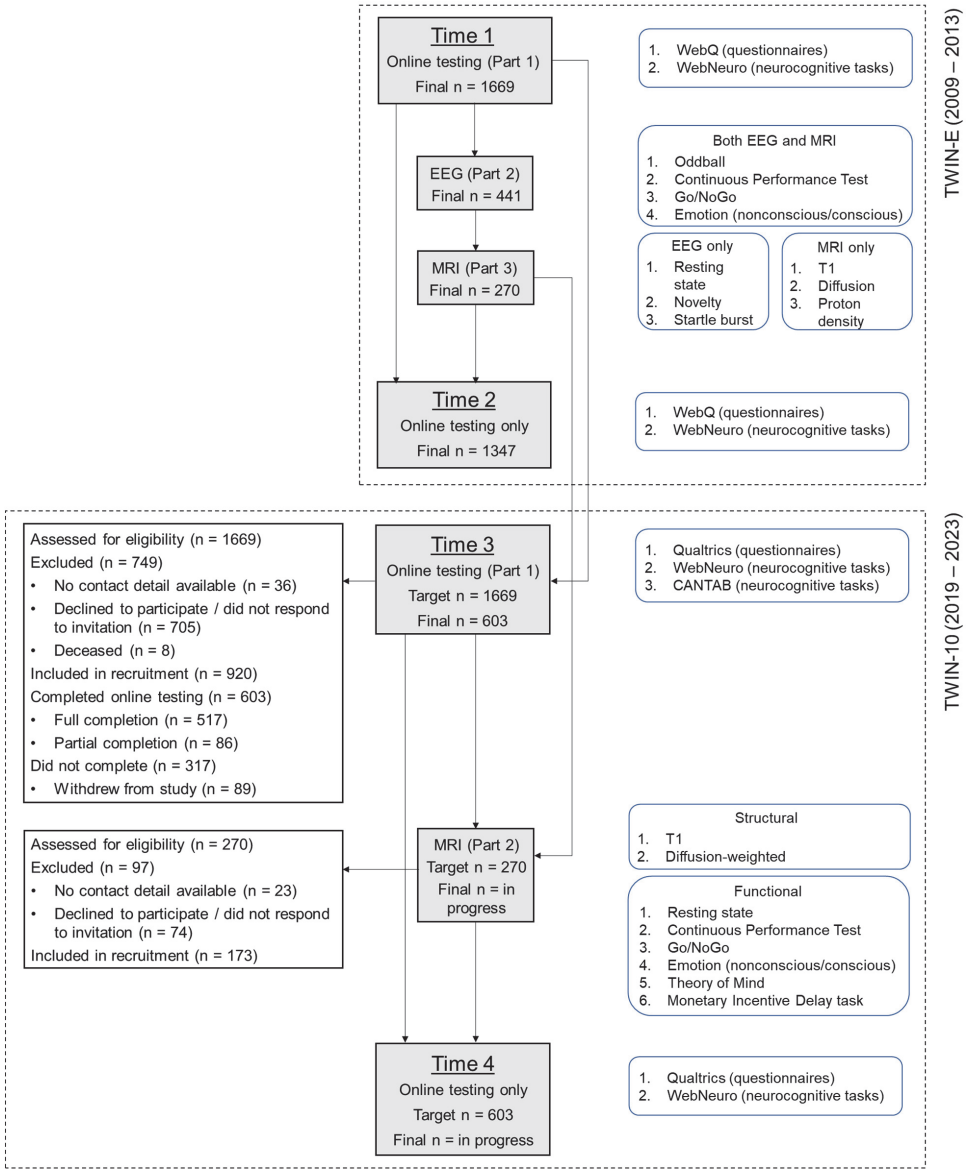

Figure 1 The TWIN project flowchart consisting of the baseline TWIN-E Study (completed) and the current TWIN-10 Study (ongoing).

considered at earlier timepoints (eg, resiliency resources, self-compassion, personality, CANTAB tasks).

Qualtrics

Self-report questionnaires were administered online via Qualtrics, and included a battery of measures assessing seven domains (general health, mental health and well-being, resilience, emotion regulation, mood and coping, personality and environmental factors; table 1).

WebNeuro

Participants were tested on their emotional and cognitive processes via WebNeuro, which is an online testing platform that provides a standardised battery of neurocognitive tasks that can be completed remotely on a personal computer at the participant's pace (table 2). Reliability and construct validity metrics have been established,[42] and the norms are provided by WebNeuro. This task was repeated across all timepoints.

Cambridge Neuropsychological Test Automated Battery (CANTAB)

The CANTAB also provides measures of neuropsychological functioning via an online testing platform and shows good reliability and validity.[43 44] Norms are provided by CANTAB. This is a new addition to the longitudinal study at time 3 and contains seven tasks that test information processing, memory and social cognition domains (table 3).

MRI measures (time 3)

MRI images were acquired using a 3T Philips Ingenia CX scanner (Philips Healthcare, Best, the Netherlands) with a 32-channel head coil at the NeuRA Imaging centre at Neuroscience Research Australia, Randwick

Table 1 List of questionnaires included in the online testing component (TWIN-E: times 1 and 2; TWIN-10: times 3 and 4)

Domain	Questionnaire	Measured at time 1	Measured at time 2	Measured at time 3	Measured at time 4
General health, lifestyle and work performance	Demographics questionnaire	x	x	x	x
	Lifestyle, nutrition, social activities and sleep[30]	x	x	x	x
	Medical history[30]	x	x	x	x
	Health and Work Performance Questionnaire (HPQ)[47]	x	x	x	x
Mental health and well-being	The Somatic and Psychological Health Report (SPHERE)[48]	x	x	x	–
	Alcohol Use Disorders Identification Test (AUDIT)[49]	–	–	x	–*
	COMPAS-W Wellbeing Scale[3]	x	x	x	x
	Abbreviated World Health Organization Quality of Life (WHOQOL-Bref)[50]	x	x	x	x
	Satisfaction With Life Scale (SWLS)[51]	x	x	x	x
	Depression Anxiety and Stress Scale (DASS-42)[52]	x	x	x	x
	PTSD checklist for DSM-5 (PCL-5)[53]	–	–	x	x
Resilience	Resilience Research Centre Adult Resilience Measure (RRC-ARM)[54]	–	–	x	x
	Ego-Resilience Scale (ER89)[55]	–	x	–	–
Emotion regulation	Self-Compassion Scale – Short Form (SCS-SF)[56]	–	–	x	–
	Emotion Regulation Questionnaire (ERQ)[57]	x	x	x	x
	Toronto Alexithymia Scale (TAS-20)[58]	–	–	x	–
Mood and coping	Internal Control Index (ICI)[59]	x	x	–	–
	Brain Resource Inventory of Social Cognitions (BRISC)[60]	x	x	–	–
	Modified Differential Emotions Scale (mDES)[61]	–	x	x	x
	Abbreviated Coping Orientation to Problems Experienced Inventory (Brief-COPE)[62]	–	–	x	x
Personality	NEO Five-Factor Inventory (NEO-FFI)[63]	x	x	x	x
	Short Oxford-Liverpool Inventory of Life and Experiences (sO-LIFE)[64]	–	–	x	–
	Temperament and Character Inventory (TCI)[65]	–	–	x	–
	Highly Sensitive Person scale (HSP)[66]	–	–	x	–
	Vividness of Visual Imagery Questionnaire (VVIQ)[67]	–	–	x	–
	Mindful Attention Awareness Scale (MAAS)[68]	–	–	–	x
Environmental factors	Daily life events questionnaire, including COVID-19-specific items[30]	–	x	x	x
	Early Life Stress Questionnaire (ELSQ)[69]	x	–	–	–
	Measure of Parental Style (MOPS)[70]	x	–	–	–

*Alcohol usage-related questions were incorporated into the lifestyle, nutrition, social activities and sleep measure at time 4.

Table 2 List of WebNeuro emotion and cognitive processing tasks included in TWIN-E and TWIN-10 (times 1–4)

Domain	Subdomain	Task	Dependent measure
Emotion	Emotion identification	Explicit emotion identification	Reaction time for each emotion* Accuracy for each emotion*
	Emotion recognition	Implicit emotion recognition	Reaction time for each emotion* Accuracy for recognition of previously seen face
Thinking	Response speed	Motor tapping	Number of taps Variability of pause between taps
		Choice reaction time	Average response time Variability of response times
	Impulsivity	Go-NoGo	Reaction time False negative/positive errors Accuracy
	Sustained attention and concentration	Continuous performance test	Reaction time False negative/positive errors Accuracy
	Information processing efficiency	Switching of attention	Completion time Errors
		Verbal interference (Stroop task)	Total number of correct 'colour' responses Total number of incorrect 'word' responses
	Memory	Digit span	Total number of digits recalled
		Memory recognition	Number of words remembered Number of intrusions (incorrect words selected) Learning rate
	Executive function	Maze	Total errors Overrun errors Completion time Total trials

*Emotion stimuli include facial expressions of anger, happiness, fear, sadness, disgust and neutral.

Australia. The MRI session included the acquisition of a T1-weighted structural scan using a 3D Turbo Field Echo sequence, a two times refocused diffusion-weighted scan and six sets of T2*-weighted echo-planar images for a resting-state scan and five functional tasks (table 4), which took around 75 min in the scanner. Blip up and blip down scans were also collected to correct for any magnetic field inhomogeneities for the diffusion and functional scans. Prior to the scanning session, each participant completed a practice session outside the scanner, which included detailed instructions regarding the structural and functional components of the session, and a practice run for two of the five functional tasks (Monetary Incentive Delay and Continuous Performance Test) on a laptop. Each participant was reimbursed AUD$100 for their travel costs to NeuRA. Duty of care reports will be prepared and checked by the MRI radiographer and a radiologist in case of significant incidental findings.

Data analysis

Questionnaire data from Qualtrics will be exported as .csv files for data preprocessing in R. This will include checking for missing or dummy responses, correct coding of responses and data imputation for missing data. All questionnaires will be collated into one master database that will include measurements collected earlier at times 1 and 2, matched by participant ID number. For MRI data, DICOM (Digital Imaging and Communications in Medicine) files from the scanner will be exported and converted into NIfTI (Neuroimaging Informatics Technology Initiative) files and uploaded onto a secure server hosted by NeuRA.

The primary outcome measures will be the COMPAS-W Wellbeing Scale and measures of illness symptoms (eg, Depression Anxiety and Stress Scale (DASS-42)). In order to map resilience versus risk trajectories, we will consider the presence of previous trauma exposure in participants to delineate those who may be more resilient (ie, showing increased or maintenance of satisfactory levels of well-being despite trauma exposure) from those who are less resilient (ie, showing reduced levels of well-being), as compared with 'control' participants who report no trauma exposure, while controlling for illness symptoms using the DASS-42. In this case, we are therefore suggesting that resilience may include either an increase in well-being scores or a maintenance (or non-decrease) in well-being scores when their baseline well-being score is within satisfactory levels (ie, moderate or flourishing ranges). However, maintenance of a languishing well-being score would not be considered resilient, but rather 'chronic risk' (figure 2). In parallel, should someone have a languishing well-being score at baseline but demonstrate an increase in well-being over time, this would be indicative of a 'recovery' profile. A parallel analysis will be conducted using DASS-42 score change as the

Table 3 List of CANTAB emotion and cognitive processing tasks included in TWIN-10 (time 3 only)

Domain	Subdomain	Task	Dependent measure
Emotion	Social cognition	Emotion bias tasks: 1. Happy–Angry 2. Happy–Sad	Response count for each emotion* Mean reaction time for each emotion* Bias point (proportion of trials where 'Happy' is chosen over 'Angry' or 'Sad')
Information processing	Decision-making, risk taking	Cambridge gambling task	Reaction time Decision-making quality Delay aversion Sensitivity to risk
	Executive function	One touch stockings of Cambridge	Number of choices Total latency Errors
	Attention	Intra–extra dimensional set shift	Total trials completed Total latency Errors
Memory	Visual memory	Paired associates learning	First attempt memory score Errors
	Retention and manipulation of visual information	Spatial working memory	Number of strategies used Errors
	Attention and recognition	Delayed matching to sample	Accuracy Probability of error given

*Emotion stimuli included facial expressions of happiness and anger for the Happy–Angry condition, or happiness and sadness for the Happy–Sad condition.
CANTAB, Cambridge Neuropsychological Test Automated Battery.

outcome variable, controlling for well-being. This will enable a dual-outcome approach and help consolidate understanding of risk versus resilience profiles using both illness symptoms and well-being outcomes. The risk versus resilience trajectories over time will be identified using structural equation modelling (SEM), per the hypothesised trajectories displayed in figure 2. These hypothesised trajectories of well-being change were adapted from prototypical patterns of disrupted functioning normally observed in individuals following trauma, as discussed by Bonanno and Loss[45] (figure 2). The trajectories of trauma response will be considered for both childhood trauma (prior to time 1) and adult trauma (10 years prior to time 3). Using these profiles, predictors of response will then be examined using linear mixed models and structural equation modelling of the different predictors over time. The predictors may include, for example, measures of emotion regulation, personality and neuropsychological performance (WebNeuro and CANTAB). Potential moderators will include factors such as resiliency resources and coping strategies. We will covary for twin-pair correlation, as well as other relevant covariates such as age, sex and zygosity. Software packages for these analyses will include linear mixed models in R or SPSS Version 26, and structural equation modelling using the lavaan package in R, the PROCESS macro in SPSS or the AMOS package in SPSS.

MRI analyses investigating corresponding changes in the brain over time will be run using SPM12 for structural and fMRI data, MRTrix3 for diffusion-weighted data and R/SPSS for statistical analyses. For cross-sectional fMRI analyses, we will use both whole-brain and regions-of-interest approaches to link task-related brain activity to neuropsychological data using a mass univariate approach, and also use multivariate independent component analysis and functional connectivity methods for task and resting-state data. Similarly, both univariate (voxel-based morphometry) and multivariate (source-based morphometry) approaches will be used for structural data, in order to uncover anatomical correlates of neural functioning. For diffusion data, we will use the MRTrix3 toolbox for white matter analysis including fibre tractography, fixel-based analysis and structural connectivity analysis. For longitudinal analyses, we will use the Sandwich Estimator Toolbox implemented in Matlab and SPM12, which takes into account within-subject correlation observed in longitudinal data and allows for a more accurate estimation of the parameters of interest.[46] We will also combine extracted structural and functional measures (eg, beta estimates, brain volume, loading coefficients) with neurocognitive measures to build a more comprehensive SEM path model, and examine the relationships between brain and behaviour that ultimately give rise to risk versus resilience and variation in well-being scores.

Finally, heritability of measures of interest (both neural and neurocognitive) will be assessed using univariate ACE twin modelling (A: additive genetic variance; C: common environment; E: non-shared environment) of MZ and DZ twin pairs, while multivariate twin models (eg, correlated

Table 4 List of structural and functional MRI tasks included in TWIN-E (time 1) and TWIN-10 (time 3) sessions

Domain	Type	Scan protocol*	Description/task	Time 1	Time 3
Structural	T1	TR=7.2 ms; TE=3.4 ms; FOV=240 mm; flip angle=8°; 190 sagittal slices; voxel size=1×1×1 mm; scanning time=3 min and 7 s	Grey/white matter volume, cortical thickness, cortical surface area	x	x
	Diffusion	TR=8300 ms; TE=78 ms; multiband acceleration factor=2; SENSE=2.5; FOV=240 mm; flip angle=90°; 58 transverse slices; voxel size=2.5×2.5×2.5 mm; 61 directions with b values of 0 and 2400; scanning time=8 min and 53 s	White matter diffusivity measures (eg, fibre density, cross section, density and cross section)	x	x
Functional	Resting state	TR=1000 ms; TE=30 ms; multiband acceleration factor=4; SENSE=2; FOV=230 mm; flip angle=62°; 68 transverse slices; voxel size=2.4×2.4×2.4 mm; 330 volumes; scanning time=5 min and 35 s	Functional connectivity measures (eg, seed to voxel, voxel to voxel, independent components analysis)	–	x
	Continuous Performance Test (CPT)	TR=2000 ms; TE=30 ms; multiband acceleration factor=2; SENSE=3; FOV=230 mm; flip angle=75°; 68 transverse slices; voxel size=2.4×2.4×2.4 mm; 157 volumes; scanning time=5 min 22 s	120 stimuli are presented (letters: B, C, D or G) for 200 ms each (ISI=2300 ms). 80 of the letters are in yellow, with 60 to be held in working memory (no consecutive repetition) while 20 are 1-back sustained attention stimuli (same yellow letter is repeated consecutively). 40 of the letters are in white, providing a perceptual baseline	x	x
	Go-NoGo	See CPT protocol	180 Go stimuli (word 'PRESS' in green) and NoGo stimuli (word 'PRESS' in red) are presented for 500 ms each (ISI=750 ms)	x	x
	Monetary Incentive Delay task	See CPT protocol; 307 volumes; scanning time=10 min and 22 s	60 trials consisting of a cue-target structure are presented. Cue options include 'win money', 'win nothing', 'lose money' and 'lose nothing', and are presented for 2000 ms (ISI=4000 ms—target duration). Target duration was variable and was determined by a staircase procedure	–	x
	Theory of Mind	See CPT protocol; 196 volumes; scanning time=6 min and 40 s	Ten video clips showing shapes either mentally interacting with each other or randomly moving are presented for 20 s (IBI=15 s)	–	x
	Emotion (masked 'non-conscious', then unmasked 'conscious')	See CPT protocol	240 images of emotional face expressions (happy, angry, sad, disgust, fear, neutral) are presented in a block design (5 blocks per emotion with each block containing 8 images of the same emotion) for: 'non-conscious'=16 ms each replaced by a neutral face for 150 ms (ISI=1084 ms); 'conscious'=500 ms each (ISI=750 ms)	x	x
	Oddball	Time 1 only; see Gatt *et al*[30] for protocol	20 target (1000 Hz) and 100 non-target (50 Hz) tones presented consecutively for 50 ms at 75 db (ISI=2.4 s)	x	–

*Scan protocol listed here is for TWIN-10 (Time 3) only; please see Gatt *et al*[30] for the TWIN-E (time 1) scanning protocol.
FOV, field of view; IBI, interblock interval; ISI, interstimulus interval; SENSE, sensitivity encoding; TE, echo time; TR, repetition time.

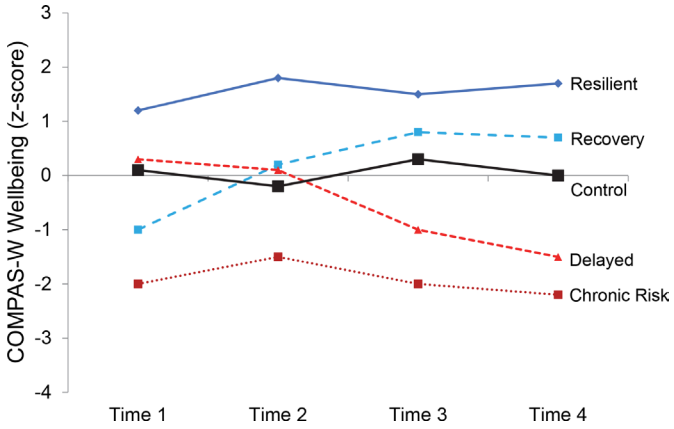

Figure 2 Predicted trajectories of risk versus resilience across the four timepoint measurements. In participants with trauma exposure, increasing or maintaining levels of well-being (indexed by COMPAS-W) will indicate resilience or recovery (differentiated by baseline well-being levels), while decreasing well-being over time may lead to delayed or chronic risk for mental illness. Control participants (without any trauma exposure) are expected to maintain their well-being levels over time. Both childhood trauma (prior to time 1) and adult trauma (over 10 years prior to time 3) will be considered. Figure adapted from Bonanno and Loss.[45]

factors models) will be used to look at the shared vs unique genetic and environmental correlations between measures. These twin models will be implemented using the OpenMx package in R. Statistical significance will be set at $p<0.05$ for all analyses, and will be corrected for multiple comparisons using Bonferroni correction for statistical data and family-wise error for MRI data.

Patient and public involvement

Participants and the general public were not involved in the design or conduct of this study as it is a longitudinal study involving repeated measurements from the 2009 baseline study.

DISCUSSION

The primary objective of the TWIN-10 longitudinal twin study is to identify trajectories of risk versus resilience over time, and the corresponding biomarkers that predict these trajectories. Despite the fact that over 75% of the Australian population will experience at least one major trauma in their lifetime, we do not yet fully understand the neural and behavioural factors that underlie resilience and mental well-being, nor the pathways in which genetic and environmental variables modulate neural circuitry to determine individual differences. Identification of such factors will be crucial in delineating the factors that ultimately lead to positive or negative mental health outcomes.

There are several strengths to the current study. By following life trajectories of a twin cohort over 12 years using structural equation modelling, we can provide robust directional evidence of neurocognitive and neuroimaging changes over time, and derive objective and observable biomarkers that may be used to calculate 'risk' for developing mental illness in individuals with previous trauma exposure in the absence of overt clinical symptoms. Additionally, by using a twin design, we can examine the extent to which neural and behavioural markers may be influenced by a person's genetic background or by environmental factors during development. The results will ultimately contribute to the development of tailored interventions that are personalised to the individual and target specific markers that are strongly predictive of well-being and resilience change.

Limitations of the current study include participant retention, which is particularly difficult over such a long period of time. In order to mitigate this, TRA keep regular records of contact details of their participating twins and so with their support, we hope to maximise our retention rates over time. Furthermore, our sampling population is limited to Australian twins with European ancestry in order to minimise the effects of genetic stratification and who are active in volunteering for research studies, which may preclude some of the findings from being generalisable across other ethnic populations, and/or singleton (ie, non-twin) groups. Despite these limitations, the benefits of using a twin sample certainly supersede these drawbacks by providing a rich dataset to evaluate the specificities of genetic vs environmental contributions.

ETHICS AND DISSEMINATION

TWIN-10 was approved by the University of New South Wales Human Research Ethics Committee (HC180403) in July 2018. Informed consent is obtained from all participants who are provided with a detailed Participant Information Sheet containing relevant information regarding each stage of the project. Each participant is provided with a unique participant identification code that is used for data collection and analyses. Further ethical approval was sought and received for the MRI component of the project by the Scientific Management Panel of Neuroscience Research Australia Imaging (CX2019-05) in July 2019.

Results of the project will be communicated to the public through various types of media, including social (eg, Facebook, Twitter), print (eg, online websites, newspapers) and broadcast (eg, television and radio) channels, as well as advertised on institutional websites (eg, NeuRA, UNSW, TRA). Findings will be published in peer-reviewed publications and presentations (including seminars, lectures, and webinars) to both the public and the academic community. All major findings will also be summarised and made available by TRA (eg, via their website, newsletter and/or email subscriptions) and emailed to participants.

Contributors HP is the postdoctoral fellow on the project, and set up the online testing and MRI components of the study, drafted the first copy of the manuscript and is currently responsible for participant recruitment and MRI data processing of the TWIN-10 project. JG conceptualised and designed the TWIN-10 Study, obtained funding from the National Health and Medical Research Council (NHMRC)

(1122816) as lead investigator and edited the first draft of the manuscript. JG is leading the project, and has contributed to all parts of the TWIN-10 project. LW and RT contributed to the study design and are coinvestigators on the NHMRC grant.

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Competing interests JG is a stockholder in MAP Biotech. LW has received advisory board fees from One Mind Psyberguide and the Laureate Institute for Brain Research unrelated to this study. HP and RT declare that they have no conflicts of interest.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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