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Research Report

AN "INTEGRATIVE NEUROSCIENCE" PLATFORM: APPLICATION TO PROFILES OF NEGATIVITY AND POSITIVITY BIAS

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The aim of the paper is to describe a standardized "Integrative Neuroscience" Platform that can be applied to elucidate brain-body mechanisms. This infrastructure includes a theoretical integration (the INTEGRATE Model). To demonstrate this infrastructure, hypotheses from the INTEGRATE Model are applied in an example investigation of the cognitive, brain and body markers of individual differences in the trait characteristic of Negativity Bias (the tendency to see oneself and one's world as negative). A sample of 270 healthy participants (18–65 years old) were grouped into equal sized matched subsets of high "Negativity Bias" and high "Positivity Bias" ($n = 135$ in each group). Participants were assessed using a standardized battery of psychological traits, cognition and brain and body (autonomic) activity. Greater "Negativity Bias" relative to "Positivity Bias" was characterized by greater autonomic reactivity and early neural excitation to signals of potential danger, at the timescale of Emotion (< 200 ms). Concomitantly, there was a relatively lower level of "Thinking", reflected in cognitive dimensions and associated electrical brain measures of working memory and EEG Theta power. By contrast, Negativity and Positivity Bias did not differ in levels of emotional resilience and social skills at the longer time scale of Self Regulation. This paper provides a demonstration of how an Integrative Neuroscience infrastructure can be used to elucidate the brain-body basis of trait characteristics, such as Negativity Bias, that are key indicators of risk for poor well-being and psychopathology.

Keywords: Integrative neuroscience; negativity and positivity bias; emotion; thinking; feeling; self regulation; electroencephalogram EEG; event-related potential ERP; cognition.

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1. Introduction

This paper serves to provide an overview of the "Integrative Neuroscience" Platform that has been established with the Brain Resource International Database [BRID; 5–7] and an independent scientific network, BRAINnet.

Drawing on the platform of Integrative Neuroscience [5–7], a theoretical framework has been proposed that bring together organizing principles and brain, body, genetic and behavioral information across scales of function and disciplines. In order to integrate information from these sources, a standardized set of protocols and tasks has been established to operate in an identical manner across multiple sites globally. These assessments provide a global standard for brain information.

The BRID is a centralized library that uses neuroinformatics platforms to integrate these sources of information. BRAINnet scientists have independent access to an academic version of the BRID in order to freely test and publish outcomes from hypothesis-driven questions.

The theoretical framework (known as the INTEGRATE Model) highlights a key organizing principle of the brain: the adaptive motivation to minimize danger and maximize reward.

This paper reports on an exemplar of how this Integrative Neuroscience platform may be applied to study the construct of "Negativity Bias" and its cognitive and brain-body correlates.

The Integrative Neuroscience Platform was developed for the integration of theory, multi-modal assessments, the collation of data in a database, the translation of these assessments into solutions for well-being, and the validation of this infrastructure via an independent scientific network (BRAINnet) (Fig. 1).

Each of the five levels of the Integrative Neuroscience Platform are outlined in turn in the following sections.

1.1. *Integration of theory: The INTEGRATE Model*

The brain is highly interconnected. However, the focus of most models of brain functioning is on the microscopic scales of single genes, neural function, and processing within highly specialized networks. While this detailed information is vital, there are limits on the extent to which mechanisms operating at a microscopic scale can be extrapolated into useful models of the whole brain.

To date scientific effort to understand brain function has been fragmented. This is changing as multidisciplinary efforts are breaking down boundaries and serving to encourage collaboration, and formulate and test models of the whole brain, that bring together key organizing principles across scale [6].

The brain model used as a frame of reference in the present infrastructure is the INTEGRATE Model (Fig. 2) which was formulated from a data-driven evidence base and an Integrative Neuroscience approach (e.g., [5, 24]). This model is based on the core motivations to minimize danger and maximize reward. Using this organizing

Fig. 1. Outline of the Integrative Neuroscience Platform. The five levels are: (1) Integration of neuroscience theory across disciplines in the INTEGRATE Model; (2) Standardized assessment protocols for psychological, cognitive, brain-body function and genetics that address each scale of brain function; (3) Collation of thousands of datasets acquired using these standardized assessments into the Brain Resource International Database (BRID); (4) Identification of Markers for health and disorder, and their translation into solutions for well-being; (5) Independent published evidence-based for this platform from an international scientific network (BRAINnet).

principle, the INTEGRATE Model proposes a dynamical continuum that spans nonconscious to conscious processing (Fig. 2).

The INTEGRATE Model brings together a number of theories across disciplines and scales of function. It is differentiated by its integration of the following concepts that are traditionally presented as dichotomous:

(1) Cognition and emotion. In the INTEGRATE Model, cognition is an overarching construct that encompasses all aspects of brain and information processing, including emotion.
(2) Nonconscious and conscious processing. Nonconscious and conscious processing of information are conceptualized as part of a temporal continuum, in which brain-body feedback is crucial to supporting the emergence of conscious awareness.
(3) Cortical and subcortical brain networks. While a neuroanatomical division has typically been used to distinguish different functions (e.g., Nonconscious

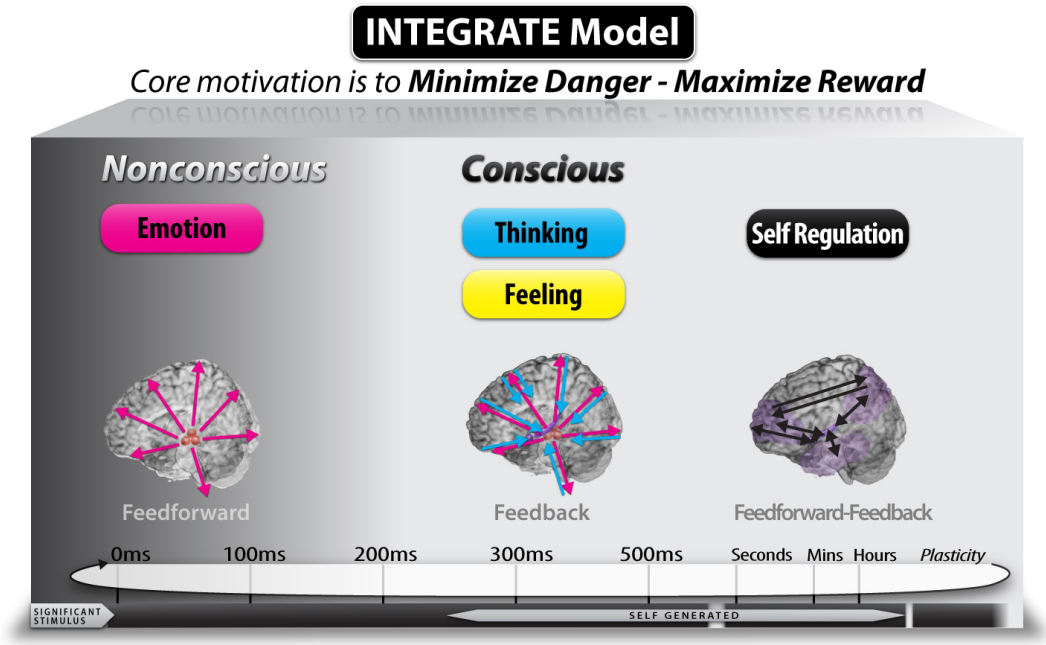

Fig. 2. The INTEGRATE Model proposes a dynamical continuum of brain organization. In this model, the core motivation to Minimize Danger-Maximize Reward is the key organizing principle of the brain. It drives Emotion, Thinking and Self Regulation along a continuum of time and associated brain and body activity. At early time scales (< 200 ms), Emotion is reflected in "action tendencies" that are triggered automatically and nonconsciously by basic signals of potential danger or reward. They can be triggered by low level signals that leave only a brief sensory trace. Action tendencies of Emotion are reflected in automatic sensory-motor repertoires, a fast latency "feedforward" mode brain activity, direct body arousal innervation, and rapid-acting neurotransmitters (such as GABA-Glutamate). At longer time scales (200 seconds), Thinking and feeling emerge with "feedback" from brain and body. Feedback includes reentrant connections from higher cortical regions, and horizontal connections within regions, that support the emergence of conscious awareness. Thinking allows for initiation of voluntary actions and selective attention to significant input, which can then be transferred to longer-term memory. Thinking and feeling are modulated by monoamines (dopamine, serotonin, noradrenaline). At longer time scales of multiple seconds and longer, the capacity for self-generated processing emerges. Self Regulation is aimed at modulating thinking and feeling over time to achieve outcomes that will Minimize Danger-Maximize Reward. Self regulation brings the capacity for planned behaviors and linking of stimuli and events over time in long term memory. It relies on ongoing cycles of feedforward-feedback brain-body interactions, and involves slower acting brain chemicals, such as hormones and neuropeptides, for example, oxytocin associated with bonding. Ongoing outcomes from Emotion-Thinking-Self Regulation will produce constant adaptions and learning in brain-body and behavior. These adaptions are reflected in brain "plasticity" and will allow some processes to become routinized as new habits.

processing = subcortical networks, Conscious processing = cortical networks), we highlight the importance of the mode of brain connectivity, rather than anatomy in subserving distinct functions: a feedforward mode of brain connectivity supports early nonconscious processing while ongoing cycles of feedback

and feedforward-feedback interactions underpin increasingly detailed functions of thinking and self regulation over time (Fig. 2).

(4) This view accords with specific examples, such as the presence of temporal organization in the visual system that does not necessarily follow its neuroanatomical hierarchy.

(5) Spatial and temporal dimensions of information processing and neural systems. Research has typically focused on either the spatial neuroanatomical basis or the temporal basis of cognitive functions. The INTEGRATE Model brings together these dimensions within the one framework, since each contribute simultaneously in complementary ways to cognitive functions.

(6) Brain and body activity. The brain and body are typically studied in isolation, yet body activity and brain-body interactions are crucial to cognitive functions. For instance, body feedback is essential to the subjective feeling of emotions. In the INTEGRATE Model, both brain and body activity are considered, and may be tested using the standardized infrastructure that allows for simultaneous recording of brain-body activity.

In addition to the core motivational principle of Minimize Danger-Maximize Reward, the temporal continuum underlying the INTEGRATE Model is captured by three key phases of information processing: Emotion, Thinking and Self Regulation (Fig. 2). This principle and constructs are defined as follows:

"**Minimize Danger and Maximize Reward**". This principle drives brain-body-behavior organization by determining what is significant to each one of us, at each point in time. The INTEGRATE Model makes explicit the manner in which key cognitive processes of Emotion, Thinking and Self Regulation interact in parallel along the processing continuum.

"**Emotion**" — Emotions are adaptive action tendencies that are mobilized by signals of potential danger or reward. They involve a "feedforward" mode of brain and body activity that is triggered automatically and without the need for conscious awareness of the triggering signal.

At longer time scales (from a fifth of a second to seconds), brain-body "feedback" supports the emergence of conscious awareness and the capacity for Thinking (and feeling) and Self Regulation.

"**Thinking**" — and feeling rely on conscious awareness, and a "feedback" mode of brain-body activity. Thinking is when you are consciously aware of information and can represent it to yourself in words or images. Feeling is when you are aware of the emotion you are experiencing and can describe it to yourself. Thinking and feeling allow us to selectively attend to information, extract its context, make controlled voluntary responses, and link these to what we know and remember.

While Emotions may proceed nonconsciously (feedforward mode), Thinking and feeling rely on conscious awareness (feedback mode).

Self Regulation is the modulation of thinking, feeling and behavioral responses to minimize danger-maximize reward over time and is inextricably linked to our wellbeing.

The INTEGRATE Model is used to generate explicit hypotheses concerning normative cognition and brain-body functioning, and the genetic and constitutional dispositions that contribute to individual differences in Emotion, Thinking and Self Regulation. These hypotheses and their implications to mental health are also being tested. These studies are being undertaken within the independent international consortium of scientists, making up the Brain Research and Integrative Neuroscience Network (BRAINnet) (see details in later section).

1.2. *Integration and standardization of assessments*

Typically, neuroscience studies are undertaken using a particular measure and customized protocol design for each new study, to target a particular scale of function (e.g., psychological function, cognition, electrical brain activity or brain blood flow). A key challenge facing neuroscience is how to pool insights from the accumulating findings across individual studies.

As part of the Integrative Neuroscience platform, a set of standardized assessment batteries have been developed, that allow for different levels of function to be assessed within the same subjects. All aspects of hardware, software, experimental protocols and data quantification are undertaken in an identical fashion. This standardization allows information to be captured in an identical way across studies and across sites. It can then be integrated to compare findings from the testing of individual hypotheses within the same standardized framework. A large set of data acquired using these assessments has formed the Brain Resource International Database (details in subsequent section).

These testing platforms have been applied in discovery research, clinical trials and in solution applications in healthcare, corporate and peak performance settings.

The standardized assessments developed by Brain Resource may be implemented as "stand alone" modules or as an integrated platform combining each of the modules:

WebQ — an internet-based battery assessing illness history, demographics and psychological function. Can be used for assessing inclusion/exclusion criteria and specific aspects of well-being. It includes assessment of personality, well-being (such as depression, anxiety, stress, early life stress, sleep) and emotional intelligence.

BRISC — (Brain Resource Inventory of Social Cognitions). The BRISC assessment of social cognitions uses a standardized self-report format.

IntegNeuro — a touchscreen-based neuropsychological test battery for assessing general cognition, that has been validated against traditional paper-and-pencil tests [4]. **WebNeuro** — a web-based version of IntegNeuro, with established validity between these platforms [18].

LabNeuro — Standardized assessment of EEG, event-related potentials (ERPs) and concurrent autonomic measures (heart rate, skin conductance and EMG) during both resting and task activation conditions. Activation tasks include the Startle, Working Memory and Facial Expression of Emotion (tasks employed in the present study) [21].

MRI-Neuro — Encompasses structural magnetic resonance imaging (MRI) for high resolution brain anatomy (with MPRage, Dual Echo sequences), Diffusion Tensor Imaging (DTI) to examine white matter connectivity and functional MRI (fMRI) activation tasks corresponding to those used in LabNeuro to assess regional blood oxygenation.

Molecular-Neuro — Standardized protocols for collection of DNA via saliva samples (and in some cases bloods) for extraction of SNPs and in selected studies, gene expression, proteomics, metabolomics and other molecular variants of interest which might impact neurocognition.

In the application of these standardized assessments, reports are generated that provide information on performance relative to the norms from the BRID.

1.3. *Brain Resource International Database*

Using the standardized assessments above, data for thousands of healthy participants and individuals from clinical groups has been acquired to form the Brain Resource International Database (BRID). The standardized nature of the assessments has enabled the data to be collated into the centralized library, that is the BRID. The BRID contains data from sites in the USA, Europe, Africa, and Australasia.

The BRID is the only integrated database of its kind. It currently contains 25 000 datasets, spanning the assessment batteries outlined above. The clinical groups encompass Depression, Schizophrenia (first episode and early onset), Bipolar Disorder, Attention Deficit Hyperactivity Disorder (ADHD), Post Traumatic Stress Disorder (PTSD), Panic Disorder, Anorexia Nervosa, Sleep Apnea, Mild Cognitive Impairment (MCI), Alzheimer's Disease and Conversion Disorder.

While typical studies in neuroscience employ around 20 participants using a customized protocol, the BRID allows hypotheses to be tested with selected data across scales of function in thousands of individuals. Factors such as age can be tightly constrained, while still maintaining a large sample size. In addition, questions concerning a clinical disorder may be tested in regard to specificity, by comparing the group of focal interest with other clinical groups in BRID.

The BRID continues to grow in several ways. First, Brain Resource continues to add to both the healthy participant pool and to new targeted groups. In addition to the clinical groups, data are being added for pre-post treatment assessments. Second, scientists using Brain Resource assessments for independent discovery research may contribute their data to the database, and thus have access to larger control groups

and other comparison groups.[a] These contributions are overseen by BRAINnet, such that the scientists remain involved in decisions about how the data may be used subsequently. There is also the opportunity to establish specific sub-databases that are more proprietary in nature, as part of a partnership model.

1.4. *Translation into solutions*

The evidence base from studies and analyses using the BRID is growing rapidly, and these insights have enabled the translation of findings into targeted solution applications, including markers of well-being, resilience in the workplace, peak performance, brain training and treatment prediction of the right drug for the right person ("Personalized Medicine") [8].

1.5. *Independent scientific network: BRAINnet*

Establishment of the BRID was undertaken in collaboration with scientific partners. The convenor (LW), and key scientists involved in the collaboration with BRID, established an independent scientific network; Brain Research and Integrative Neuroscience Network, BRAINnet; (http://www.BRAINnet.net). The BRID has been made available for free in the form of quantified data to BRAINnet, for testing and scientific publication of hypothesis-based outcomes.

BRAINnet has grown rapidly since its establishment in 2003, to over 180 scientific members. The milestone of 150 peer-reviewed publications was reached in 2007 (total 187). On average, one publication was published per week in 2007/2008.

While the majority of members continue to contribute data to the BRID via new discovery projects (which is turn is made available to BRAINnet), there is also a growing membership that access the data to test specific hypotheses without contributing new data. The value of this mixed model for all members is that it means that the data may be used to test new hypotheses that would not otherwise be examined by another group of scientists. BRAINnet membership has agreed on a set of guidelines for requesting data and publication.

1.6. *Application to Negativity Bias and correlates*

The construct of Negativity Bias is one of the key social cognition markers and is an appropriate exemplar in testing the INTEGRATE Model, given the motivation is to minimize danger. Negativity Bias reflects the tendency to perceive stimuli, oneself and events in the world as relatively more negative than positive. This marker accords with similar constructs of processing biases identified in the social psychological and psychophysiological literature [1, 9, 16, 19, 26].

[a]Of course, the professionals using these assessments in applied settings control the data they acquire, and may choose not to contribute scores to the database.

It has been demonstrated that the general absence of traits of Negativity Bias reflects a Positivity Bias [16]. In this study, we define groups according to a high versus low Negativity Bias — defined as "Negativity Bias" and "Positivity Bias" groups.

In the INTEGRATE Model, Negativity Bias is considered to be both on the genetic predisposition to Minimize Danger and the Self Regulation timescale, given that it varies over days and weeks. However, evidence to date suggests that traits of Negativity Bias impact information processing over earlier timescales of Emotion and Thinking [19, 21], by facilitating a relatively greater (or lower) focus on negative danger-related input. Thinking functions such as selective attention to non-threat related signals and tasks may also be disrupted with a higher Negativity Bias. A higher Negativity Bias may also impact other self regulatory functions, such as social skills [9].

In this study, we assessed whether Negativity Bias was distinguished from Positivity Bias in terms of markers of Emotion and Thinking, and related markers of Self Regulation. These markers included measures of psychological, cognitive and brain-body functions.

2. Methods

2.1. *Participants*

An initial pool of 1684 healthy participants (18–65 years) were recruited from the Brain Resource International Database [BRID; 5]. Exclusion criteria included Axis I mental illness, neurological disorder or other serious medical condition, brain injury or loss of consciousness for 10 minutes or more and substance dependence (smoking, alcohol and other drugs). From this pool, we identified equal sized groups ($n = 135$ each) of participants according to those scoring low (< 1 sd below the mean) and high (> 1 sd above the mean) on the measure of Negativity Bias (see Negativity Bias below for details of the measure).[b] For simplicity, these groups were referred to as the "Negativity Bias" and "Positivity Bias" groups, respectively. These groups were matched on demographic factors, and we confirmed that there were no significant differences in age, sex, years of education, height, handedness or weight between them. The mean age of the "Negativity Bias" group was 33.0 ± 12.8 and the mean age of the "Positivity Bias" group 33.1 ± 12.8. The mean education levels of the groups were 14.4 ± 2.5, and 15.0 ± 2.3 respectively. Each group had 73 females and 62 males. There were no significant differences in age, gender, years of education, height, handedness or weight between these derived groups. All participants gave written informed consent in accordance with national health and medical research council guidelines prior to participating.

[b]Scores on the measure of Negativity Bias are standardized (z scores), such that low scores are in the direction of greater negativity while high scores are in the direction of relatively greater positivity. These directions are consistent with scores on the cognitive measures, in which higher z scores reflect better performance.

2.2. *Negativity Bias measure*

The measure of Negativity Bias was assessed using the Brain Resource Inventory of Social Cognitions (BRISC), which has been established previously [17, 27]. It may be defined as part of the construct of social cognition, which includes the attribution and regulation of emotional and interpersonal functions. The BRISC, and domain of Negativity Bias, was established using factor analysis of measures of emotional intelligence, negative attributional traits and temperamental traits [17, 27]. BRISC items were found to form three distinct dimensions using a Principal Component Analysis (PCA) with oblimin axis rotation (delta = 0). The first dimension was termed "Negativity Bias", given that highest loading items reflected negative attributional traits associated with the tendency to see oneself and one's world as negative. These traits are associated with sensitivity to stress and regulation of emotions.

Given that the Negativity Bias domain was determined using PCA, it is quantified in terms of standardized scores (z scores). Scores are inverted such that low scores indicate an excessive Negativity Bias, and high scores a Positivity Bias. This interpretation is consistent with previous proposals that a general absence of traits such as neuroticism are associated with a generally positive view of oneself and events [16].

2.3. *Summary of Emotion, Thinking and Self Regulation markers*

Using the INTEGRATE Model, we acquired the following markers relevant to the timescale of Emotion, Thinking and Self Regulation. These markers were acquired using a battery of psychological measures (BRISC), cognitive assessments (IntegNeuro) and electrical brain and body function measures (LabNeuro), described in detail in the subsequent sections.

Emotion Markers (< 200 ms):

(1) Startle Electromyogram (EMG): Assessed with LabNeuro autonomic ("body") measures. Startle stimuli elicit early (within 120 ms) EMG activity.
(2) Resting Electroencephalogram (EEG) Alpha band frequency and power; Assessed with LabNeuro EEG. Alpha band activity (8–13 Hz) cycles approximately every 100 ms.
(3) Facial emotion Event-related potentials (ERPs); Assessed with LabNeuro Facial Expressions of Emotion Brain Activation task. Basic facial expressions of emotion (fear, anger, sadness, disgust and happiness) presented under both conscious and nonconscious perception conditions modulate early ERPs (within 200 ms) [24–26].

Thinking Markers (200 ms to seconds):

(4) General cognition: Assessed with IntegNeuro cognitive assessments. It yields composite dimensions of sustained attention, working memory capacity, verbal

memory, information processing efficiency, response speed, executive function and impulsivity [17, 11].
(5) Resting EEG Theta band activity: Assessed with LabNeuro EEG. Theta activity (4–7 Hz) cycles approximately every 250–300 ms.
(6) Working Memory ERPs: Assessed with LabNeuro Working Memory task. A working memory task, corresponding to that used in the cognitive battery modulates ERPs elicited around 450 ms post-stimulus.

Self Regulation (multiple seconds and longer):

(7) Social cognition assessed with the BRISC. Composite dimensions from the BRISC capture Emotional Resilience and Social skills (capacity for social relationship building).
(8) Heart Rate Variability; Assessed with LabNeuro autonomic ("body") measures. Heart rate variability captures regulation of sympathetic versus parasympathetic activity associated with modulating actions and attention to significant stimuli with changing situations.

The methods used to acquire these markers are outlined below:

2.4. *BRISC assessments*

Principal components analysis (PCA) of Brain Resource measures of emotional intelligence [BRIEF; 10] and personality traits using the BRISC battery have yielded two domains of social cognition, in addition to Negativity Bias [17]. These dimensions are defined as follows:

Emotional Resilience: Capacity for coping with life and feeling confident in yourself and your opinions. Related to self-esteem, self-efficacy and self-assurance.

Social Skills: Capacity for building and maintaining relationships, and understanding other people. Associated with extraversion and empathy.

2.5. *IntegNeuro cognitive battery*

General cognition assessments were part of a computerized and standardized battery; "IntegNeuro" [4]. This battery is presented using a touchscreen. Standardized instructions were presented visually on the screen and using concurrent audio files (via headphones). Reaction time and accuracy, as well as verbal responses (via a microphone and recording system attached to the headphones) were recorded. The test battery has well established psychometric properties, including test-retest reliability [21], validation against traditional paper and pencil tests [12], consistency across cultures [13] and norms by age and sex [4]. Using principal components analysis (PCA), with oblimin (delta = 0) rotation, individual cognitive tests have been

found to form seven composite dimensions of general cognition [15, 11]. These dimensions formed the "Thinking" markers of cognition, and were defined as follows:

Sustained Attention: Reaction time and errors for the n-back continuous performance test of sustained attention. Reflects attention to the main task and resisting distraction over time.

Response Speed (sensori-motor function): The number of taps and average pause between taps for a sensori-motor tapping test. It reflects psychomotor function.

Working Memory Capacity: Scores on a forwards and reverse digit span test. It reflects the capacity to hold and manipulate information "online".

Information Processing Efficiency: Scores on a visual (Part I) and verbal (Part II) interference test, duration for a switching of attention test with Part I (digits) and Part II (digits and letters), and choice reaction time. This dimension reflects capacity for complex and flexible information processing under time demands.

Verbal Processing: Number of words generated on the tests of verbal (FAS) and semantic (animal category) fluency. It reflects the fluency of verbal processing. Executive function: maze test completion time and number of overrun errors, and span of visual memory.

Verbal Memory: Immediate recall, delayed recall and memory recognition on a verbal recall test. This dimension reflects verbal learning and declarative memory.

Impulsivity: Errors, reaction time and reaction time variability on a Go-NoGo test. It reflects the balance between automatic responses and suppressing these responses as the task situation changes.

Executive Function: Completion time and overrun errors in a maze test. It reflects planning, monitoring and using feedback to adjust and organize behavior.

2.6. *LabNeuro battery*

Startle EMG

Participants were presented with a series of 20 acoustic startle stimuli (noise burst at 105 dB, 50 ms duration, instantaneous rise and fall). The startle response captures the action tendency of fear, and is reflected in the muscle contractions (assessed by EMG) of the eye-blink reflex.

Heart Rate Variability

Heart rate variability (HRV) was quantified in terms of frequency measures. Using a Welch window on the time series of inter-beat (RR) intervals, we quantified total spectral power for very low frequency (VLF: 0.003–0.04 Hz), low frequency (LF: 0.04–0.15 Hz) and high frequency (HF: 0.15–0.4 Hz), and the LF/HF ratio.

Resting EEG (power)

Subjects were asked to refrain from smoking and caffeine consumption for two hours prior to assessment. EEG data were recorded continuously from 26 scalp sites with a 500 Hz sampling rate, using a NuAmps amplifier, with Ag/AgCl electrodes and a Quikcap according to the 10–20 international system. Linked mastoids (A1, A2) were the reference.

EEG data were acquired for 2 minutes under two conditions; (1) with eyes open and (2) with eyes closed. Power spectral analysis was performed on each four second interval by first applying a Welch window to the data, and then performing a Fast Fourier Transform (FFT). The resulting power spectra were averaged for each condition for each electrode. Power was calculated for the following frequency bands: Delta (1.5–3.5 Hz), Theta (4–7.5 Hz), Alpha (8–13 Hz), and Beta (14.5–30 Hz). Resting EEG measures were log transformed in order to better approximate the normal distribution assumptions required by parametric statistical methods.

Resting EEG (peak frequency)

For Alpha activity, we also examined alpha peak frequency since it captures the speed of neural processing within the critical sub-200 ms timescale of Emotion. When viewed as a spectrum, the resting EEG is dominated by the alpha peak, occurring at about 10 Hz. It has been previously reported that the alpha peak splits into two distinct sub-peaks, in most individuals, that are separated by 1–2 Hz [2, 14, 15]. Sometimes the alpha peak appears to be the result of two largely overlapping peaks that have slightly different peak frequencies and distinguishable foci on the scalp.

Because of the overlap, the identification of two peaks is very difficult to do automatically in an accurate and unbiased way. Therefore, the newly developed SINAPS platform was used to analyze EEG Eyes Open and Closed Spectra for group differences in alpha peaks, as the SINAPS method analyses differences across the 50 Hz spectra without needing the location of any features (e.g., peaks). Regions which show statistical differences are highlighted by the method, and it is up to the researcher to visually identify which features (peaks, etc.) are present in the group waveform in any highlighted frequency window(s).

Facial Emotion ERPs

We recorded EEG data (using the NuAMPS system described above) during the Facial Expressions of Emotion Brain Activation Task [FEEBA; 22–24]. Grey scale 3-D evoked facial expression stimuli (depicting fear, anger, disgust, sadness, happiness, and neutral) were selected from a standardized set of stimuli.

A total of 96 stimuli (8 different individuals depicting each expression) were presented pseudorandomly under two conditions: Conscious perception (500 ms stimulus duration, inter-stimulus interval (ISI) 767 ms) and Nonconscious perception (10 ms duration, followed immediately by a backward mask neutral face stimulus for 150 ms, and ISI of 1107 ms). Thus, the total stimulus asynchrony was equivalent

(1267 ms) in each condition. The psychophysics for the backward masking parameters have been previously established [20].

We extracted ERPs for each emotion. The focal ERPs of interest have been previously established [24, 26]. They were the N120 (peak around 120 ms post-stimulus) and Vertex Positive Potential (VPP, peaking around 170 ms) elicited over medial fronto-central sites. Concomitant polarity-reversed EPRs over temporal and occipital sites were the P120 and N170, respectively. These ERPs were quantified in terms of peak amplitude.

Working Memory ERPs

ERPs were also extracted from the EEG recorded during a Working Memory task, corresponding to that used in the IntegNeuro battery. A series of letters (B, C, D or G) were presented to participants sequentially for 200 ms, separated by an interval of 2.5 seconds. Participants were asked to press buttons with the index finger of each hand when the same letter appeared twice in a row. There were 125 stimuli presented in total, 85 being non-target letters (to assess working memory updating) and 20 being target letters (i.e., repetitions of the previous letter, to assess sustained attention). Speed and accuracy of response were equally stressed in the task instructions. For this study, we quantified the working memory P450 ERP (peaking around 450 ms post-stimulus) to non-target stimuli, which reflect updating of working memory [3]. It was quantified in terms of peak amplitude.

2.7. *Data reduction and analysis*

ANOVA Analyses

Analysis of variance (ANOVA) was used to compare Negativity Bias and Positivity Bias groups on the selected Emotion, Thinking and Self Regulation markers (with the exception of EEG Alpha peak frequency, as outlined below). Dependent measures were each of the markers outlined in the summary of markers in Sec. 2.3. Given the exploratory nature of the exemplar application of the INTEGRATE Model to Negativity Bias, significance was determined at an alpha level of 0.05. Analyses were performed using the Statistical Package for Behavioral Science (Version 15: SPSS Inc, Chicago).

SINAPS Analyses

To analyse EEG Alpha peak frequency, outlier removal and analysis were performed using "R" version 2.7.0 available from http://www.r-project.org/. This software was implemented as a customized platform: the Standardized Integrative Neuroscience Analysis Platform Software (SINAPS). A moving contrast window was used to compare groups on the spectral time series of Alpha peak frequency in each 1 Hz or 24 millisecond bin.

A t-test of group differences was applied at each millisecond bin to determine whether group differences exceeded the critical alpha value of 0.05. This method

identifies robust differences between the group average waveforms independent of any scoring criteria or frequency bin definitions (these frequency bins are applied only subsequent to quantification to define the Alpha band for visualization purposes).

3. Results

The ANOVAs for each marker (and SINAPS analysis of EEG peak frequency) revealed a profile of significant differences between the "Negativity Bias" and "Positivity Bias" groups. The descriptive data and significant effects summarized for ANOVA analyses summarized in Table 1 and SINAPS peak frequency results presented in Fig. 4.

Group differences on the focal markers of interest are discussed in relation to their grouping under Emotion, Thinking and Self Regulation, in turn.

3.1. *Emotion marker results*

ANOVA Analyses

"Negativity" and "Positivity Bias" groups showed a consistent pattern of differences on the Emotion markers.

Table 1. Summary of means (and standard deviations) for Negativity Bias and Positivity Bias groups on the markers representing the Emotion, Thinking and Self Regulation, domains from the INTEGRATE Model. F and p values are presented for those markers that differed significantly between these groups (Abbreviations: EC = Eyes Closed, EO = Eyes Open).

INTEGRATE Model Domain	Marker	Mean (sd): Negativity Bias Group	Mean (sd): Positivity Bias Group	F Value	p Value
Emotion*	Startle EMG	4.14(4.46)	3.52(7.03)	4.87	0.009
	ERP amplitude				
	Conscious Fear P120 (T6)	4.37(3.29)	6.03(3.42)	1.34	0.017
	Conscious Anger P120 (T5)	2.78(2.71)	4.15(3.19)	6.40	0.030
	Nonconscious Fear N170 (T6)	−0.77(3.24)	−2.16(3.40)	5.38	0.017
Thinking	General cognition (z scores)				
	Sustained Attention	0.12(0.92)	0.36(0.68)	3.71	0.025
	Working Memory Capacity	−0.30(1.47)	0.22(0.89)	6.44	0.002
	Information Processing	−0.32(1.73)	0.10(0.72)	4.82	0.009
	Efficiency EEG				
	EC EEG Theta (Pz)	2.41(0.74)	2.67(0.78)	3.708	0.025
	EO EEG Theta (Pz)	2.04(0.57)	2.22(0.66)	3.133	0.045
	ERP amplitude				
	Working Memory P450 (P3)	8.59(4.06)	9.83(4.16)	4.02	0.019
Self Regulation	Heart Rate Variability				
	Eyes Open Low Frequency Measure	0.08(0.03)	0.09(0.03)	4.181	0.016

*See Fig. 4 below for SINAPS analyses of EEG peak frequency.

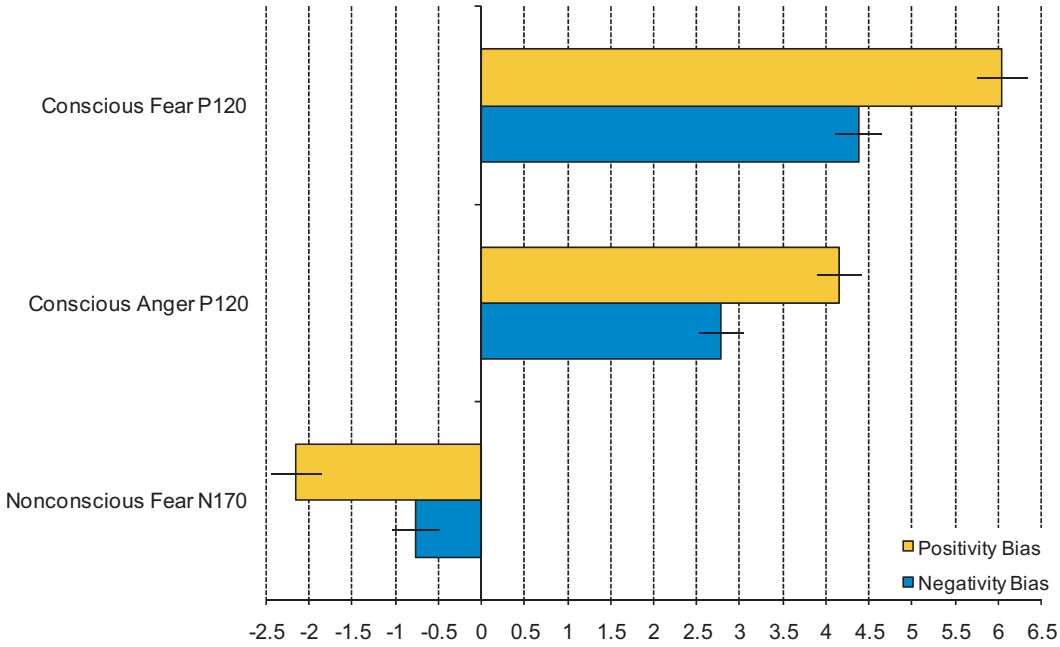

Fig. 3. "Negativity Bias" and "Positivity Bias" groups differed on ERPs elicited by the Facial Expressions of Emotion for Brain Activation task. In the conscious perception condition, the Negativity Bias group had relatively lower amplitude for the P120 for fear (right temporal cortex) and anger (left temporal cortex). For nonconscious perception, the Negativity Bias group had relatively lower amplitude for the right temporal N170 for fear. The x axis depicts amplitude in microvolts.

In terms of autonomic markers, the "Negativity Bias" group showed comparatively greater EMG reactivity to startle stimuli (Table 1). This finding is indicative of higher sympathetic arousal, consistent with relatively greater reactivity to signals of danger that elicit an action tendency of fear.

ERP markers showed further group differences at the early (< 200 ms) timescale of Emotion. Differences were specific to threat-related signals of emotion. The "Negativity Bias" group showed comparatively higher excitation (reflected in a relative reduction in the amplitude of early positivity, indexed by the temporal P120), during conscious perception of expressions of fear and anger (Table 1; Fig. 3). These P120 effects were apparent over the right temporal cortex for fear, and over the left temporal cortex for anger. In addition, nonconscious perception of fear elicited a decrease in the right temporal N170 for Negativity relative to Positivity Bias groups (Table 1; Fig. 3), suggesting that the increase in excitation is most apparent during conscious perception.

SINAPS Analyses

For EEG Alpha (at the timescale of Emotion, in which Alpha activity cycles every approximately 100 ms) there were group differences in peak frequency in particular. For the Eyes Closed condition, Negativity and Positivity Bias groups showed a

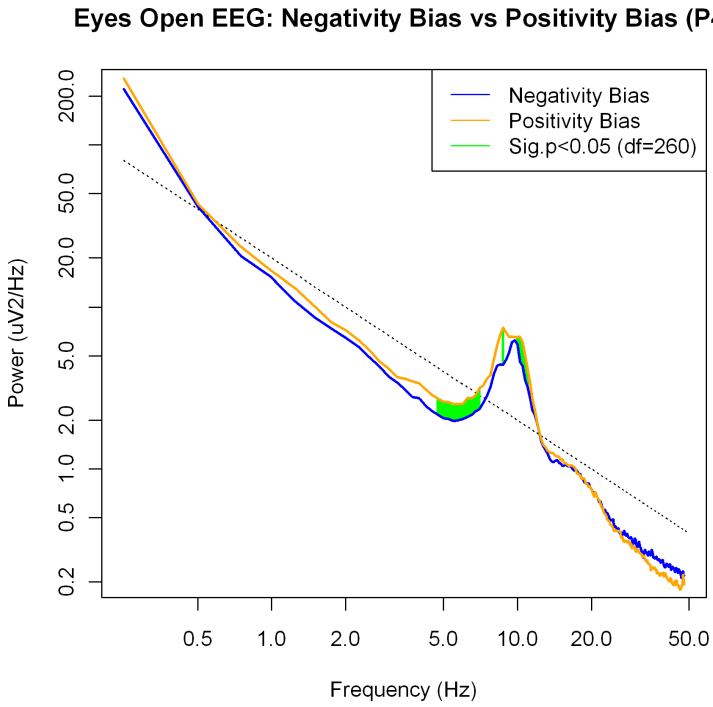

Fig. 4. Summary of results for Eyes Open Spectra SINAPS time series analysis: Data are plotted for "Negativity Bias" (blue) and "Positivity Bias" (orange) groups. Significant differences in the waveforms are colored in green. The dotted line represents the (theoretical) 1/f EEG baseline. For this condition, both groups showed a dual Alpha peak. The "Negativity Bias" group was distinguished by a larger alpha peak 2 (consistent with higher frequency and faster processing), while the the Positivity Bias group was distinguished by a larger alpha peak 1 (indicating lower frequency and slower speed). These differences were apparent across central-parietal sites (P4 as shown, and at P3, Pz, CP4, CPz).

single alpha peak. The "Negativity Bias" group showed a faster peak frequency for the Alpha peak which was apparent across a multiple sites (Fp1, F7, F3, Fz, F4, F8, FC3, FCz, FC4, C4, C3, CP3, CPz, Pz, P4, T6, O2).

For the Eyes Open condition, both Negativity and Positivity Bias groups showed a dual Alpha peak. SINAPS analysis of the time series showed that the "Negativity Bias" group was distinguished by a larger Alpha 2 peak (consistent with higher Alpha peak frequency) and the "Positivity Bias" group by a larger Alpha 1 peak (consistent with lower Alpha peak frequency) (Fig. 4). These group differences were distributed over central-parietal brain regions in particular. Higher Alpha peak frequency accords with faster thalamo-cortical speed, while lower peak frequency corresponds to slower speed.

3.2. *Thinking marker results*

For the general cognitive dimensions associated with the Thinking domain of the INTEGRATE Model, the "Negativity Bias" group showed significantly and

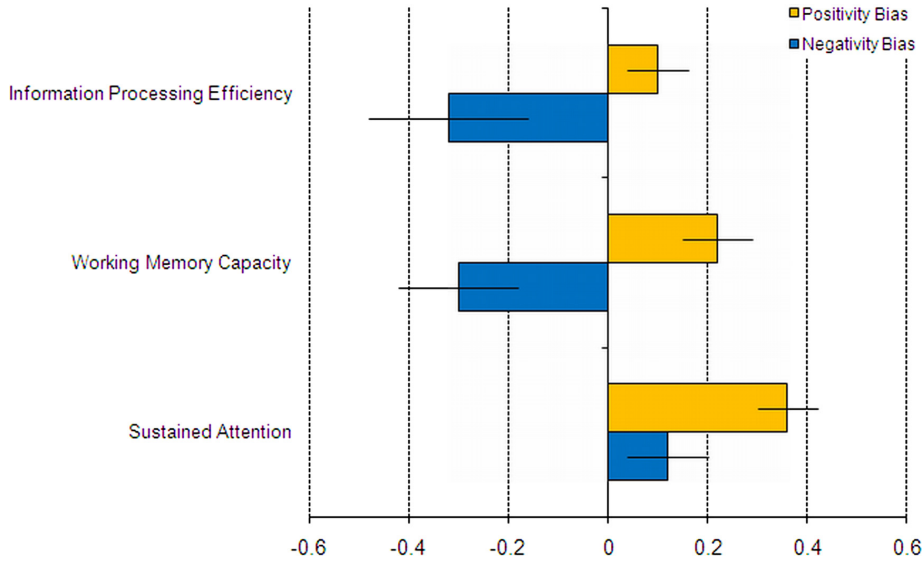

Fig. 5. Means (and standard errors) for the "Negativity Bias" and "Positivity Bias" groups in the Thinking domain for cognitive measures (in z scores) of Sustained Attention, Working Memory Capacity and Information Processing Efficiency. The "Negativity Bias" group showed significantly lower performance on these measures in the Thinking domain (see Table 1 for F and p values).

relatively lower performance than the "Positivity Bias" group (Table 1), although we note that performance in both groups was still within a normative range. Specifically, the "Negativity Bias" group had relatively lower sustained attention, working memory capacity and information processing efficiency (Table 1; Fig. 5). Relatedly, the "Negativity Bias" group also showed a decrease in the amplitude of the P450 Working Memory ERP, related to the "Positivity Bias" group (Table 1). This reduction accords with the relatively lower performance on cognitive dimensions for sustained attention (evaluated using the same n-back test) and working memory capacity (evaluated using related working memory tests).

In addition, the "Negativity Bias" group had a decrease in Theta (4–7.5 Hz) power over fronto-central sites, relative to the "Positivity Bias" group (Table 1). Theta power has been associated directly with working memory load.

3.3. *Self regulation marker results*

Notably, the Negativity and Positivity Bias groups did not differ on other trait characteristics of social cognition, including emotional resilience and social skills. This is an important null result, indicating that Negativity Bias may have specific effects on early information processing without affecting self regulation.

The one isolated result was for the heart rate variability measures, in which the "Negativity Bias" group has a small but significant reduction in the low frequency measure of variability for the resting condition (Table 1). This finding accords with the higher early autonomic reactivity.

4. Discussion

In this paper, we summarized the Integrative Neuroscience platform, which combines five levels: (i) cross-scale and cross-disciplinary theory; (ii) standardized assessments for psychological, cognitive, brain-body and molecular information; (iii) collation of data acquired with these assessments in an international data library of healthy and clinical standardization groups; (iv) identification of markers from these data to apply in brain health solutions; and (v) discovery research undertaken via an independent scientific network using the standardized assessments and data. As an exemplar of this infrastructure, the neural correlates of Negativity Bias were examined within an integrative theoretical framework, using selected theoretically-driven markers from the assessment batteries.

The INTEGRATE Model highlights the centrality of core motivations (minimize danger-maximize reward) to organizing the dynamics of information processing. While priority is given to sources of potential danger, an excessive bias towards these sources and the expectation of negative events may be maladaptive. Here, we tested the working hypotheses that a "high Negativity Bias" group would be distinguished from a "Positivity Bias" group by heightened reactivity (brain and body) to signals of potential danger, at the early timescale (< 200 ms) of Emotion. In turn, it was expected that higher early reactivity may constrain cognitive functions (such as selective allocation of attention) in the "Negativity Bias" group at the timescale of Thinking.

Consistent with working hypotheses, the "Negativity Bias" group was distinguished by a profile of comparatively faster neural activity and greater early excitation to threat-related stimuli (within 200 ms of stimulus onset). These findings were reflected in faster Alpha peak frequency (cycling every approximately 100 ms) and greater negativity in early ERPs to fear and anger stimuli, including in the absence of awareness. The neural profile associated with higher Negativity Bias may thus be one of greater readiness for automatic reactivity to significant sensory input. The focus of the early excitation in the temporal cortex is consistent with evidence that there is a direct feedforward pathway for perceiving signals of potential danger that engages early visual regions in temporal cortex [25]. This pathway is considered a "fast latency" pathway, consistent with the presence of faster thalamo-cortical speed (indexed by Alpha peak frequency) in the Negativity Bias group.

We note that faster Alpha peak frequency was apparent under resting conditions, while the early excitation was present for stimulus-related emotion processing. An increase in the neural trait of speed of processing may contribute to the enhanced vigilance for potential danger that defines the psychological trait of Negativity Bias. In turn, a neural trait of faster processing may support greater excitation in reaction to a potential danger stimulus.

The inclusion of the customized SINAPS analysis platform was valuable in revealing the findings for Alpha peak frequency, as a correlate of Negativity Bias. The

capacity to identify a dual Alpha peak in the eyes open condition provided confidence in the results; since the Negativity Bias group showed higher frequency (faster processing) on Alpha 2 in particular, which in itself is the higher frequency peak. Traditional quantification (based on averaged timeseries and "peak picking") would not typically identify the dual Alpha peak, but would rather focus on the peak with the greatest power. Future research and biophysical modeling are required to elucidate the mechanisms of the faster peak frequency with higher Negativity Bias. An avenue of exploration would be the possibility that functional mechanisms underlie this shift, such as the differential impact of neuromodulators. In the INTEGRATE Model, GABA-Glutamate are associated preferentially with the early timescale of Emotion, and monoamines with the Thinking timescale; each of these might be tested in relation to their impact on neural function according to level of Negativity Bias. Biophysical modeling may also provide convergent evidence for these neurochemical effects [14, 15].

Further support for the working hypotheses came from "Thinking" timescale markers. On the dimensions of general cognitive function, the "Negativity Bias" group showed relatively lower performance than the "Positivity Bias" group. This relative reduction was paralleled by lower EEG Theta power and a lower working memory P450 ERP in the Negativity compared to Positivity Bias group. Together, this profile of cognitive-brain function "Thinking" markers is consistent with the possibility that heighted early automatic processing may disrupt the capacity for attending and updating working memory at the slower timescale of Thinking. A previous BRID finding was a positive association between Alpha peak frequency and working memory performance for a healthy group [3]. It is possible that an excessive Negativity Bias disrupts the normal organization of processing speed (at the Emotion timescale) and working memory (at the Thinking timescale).

Notably, the Negativity and Positivity Bias groups did not differ on other trait characteristics of social cognition, including emotional resilience and social skills. This null result indicates that Negativity Bias may have specific effects on early Emotion processing and Thinking, without necessarily affecting other aspects of Self Regulation. Of course, it would also be important to further explore this issue using additional measures of trait characteristics associated with Self Regulation, and their brain-body correlates.

The example application to Negativity Bias and its correlates provides preliminary findings from which more explicit hypotheses may be generated and tested using the standardized infrastructure. BRAINnet provides the context for testing more specific hypotheses regarding the mechanisms underlying Negativity Bias. Such research will also address the real world significance of Negativity Bias in terms of predicting risk for psychopathology and decreased adaptive resilience. With the accumulation of such an evidence base, increasingly tailored brain health solutions that enable individuals to regulate their own level of Negativity Bias may be targeted.

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Disclosure

EG holds significant equity and stock options in Brain Resource Ltd, and LMW is a small equity holder. LMW has received fees from Brain Resource for work unrelated to this study. KB and NC are employed in research and development positions by Brain Resource Ltd.

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