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**Research Report**

# THE INTEGRATE MODEL OF EMOTION, THINKING AND SELF REGULATION: AN APPLICATION TO THE "PARADOX OF AGING"

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This study was undertaken using the INTEGRATE Model of brain organization, which is based on a temporal continuum of emotion, thinking and self regulation. In this model, the key organizing principle of self adaption is the motivation to minimize danger and maximize reward. This principle drives brain organization across a temporal continuum spanning milliseconds to seconds, minutes and hours. The INTEGRATE Model comprises three distinct processes across this continuum. *Emotion* is defined by automatic action tendencies triggered by signals that are significant due to their relevance to minimizing danger-maximizing reward (such as abrupt, high contrast stimuli). *Thinking* represents cognitive functions and feelings that rely on brain and body feedback emerging from around 200 ms post-stimulus onwards. *Self regulation* is the modulation of emotion, thinking and feeling over time, according to more abstract adaptions to minimize danger-maximize reward. Here, we examined the impact of dispositional factors, age and genetic variation, on this temporal continuum. Brain Resource methodology provided a standardized platform for acquiring genetic, brain and behavioral data in the same 1000 healthy subjects. Results showed a "paradox" of declining function in the "thinking" time scale over the lifespan (6 to 80+ years), but a corresponding preservation or even increase in automatic functions of

"emotion" and "self regulation". This paradox was paralleled by a greater loss of grey matter in cortical association areas (assessed using MRI) over age, but a relative preservation of subcortical grey matter. Genetic polymorphisms associated with both healthy function and susceptibility to disorder (including the BDNFVal$^{66}$Met, COMTVal$^{158/108}$Met, MAOA and DRD4 tandem repeat and 5HTT-LPR polymorphisms) made specific contributions to emotion, thinking and self regulatory functions, which also varied according to age.

*Keywords*: Integrative neuroscience; genetic polymorphism; age; emotion; thinking; self regulation; cognition; MRI; EEG and ERPs; psychiatric disorder.

## 1. Introduction

Since the Decade of the Brain (a congressional initiative for the 1990s) and the rapid development of human neuroscience, there has been an explosion of sub-disciplines, focused on specific aspects of brain structure or function at microscopic or whole-brain scales. "Integrative Neuroscience" [23, 24] offers a framework for considering the essential organizing principles that operate across these sub-disciplines and scales, including links between the different sources of brain and genetic information. From this approach, we have articulated an integrative continuum model of brain organization [26, 77, 81].

In this model, the most fundamental principle for brain organization is our basic motivation to minimize danger and maximize reward. This principle drives the organization of information processing across time scales, and the preferential engagement of associated brain and body systems. At short time scales, the minimize danger-maximize reward principle determines priority to threat-related signals, while at long time scales more abstract formulations of this principle determine the priority with which we regulate and plan our behaviors.

Individual variations in the organization of information processing across this temporal continuum may be contributed by genetic disposition and its ongoing role in the plasticity of the brain as it adapts to the outcomes of processing over time. Constitutional factors such as age may also contribute to such variation, reflecting the effects of maturation, development and aging. Both genetic variants and age also play a role in susceptibility to mental disorder and the associated disruptions in brain organization.

Here, we first examined the impact of age on cognitive, brain function and brain structure measures capturing the temporal continuum of emotion, thinking and self regulation. We then examined the contribution to these measures, of genetic variants implicated in information processing across these time scales, and involved in modulating monoamines (serotonin, dopamine, noradrenalin) and synaptic plasticity.

### 1.1. *INTEGRATE model*

Based on the platform of integrative neuroscience, we have developed the "INTEGRATE Model". This model is summarized in Fig. 1. It is intended as a cross-disciplinary and cross-scale frame of reference to bring together traditionally

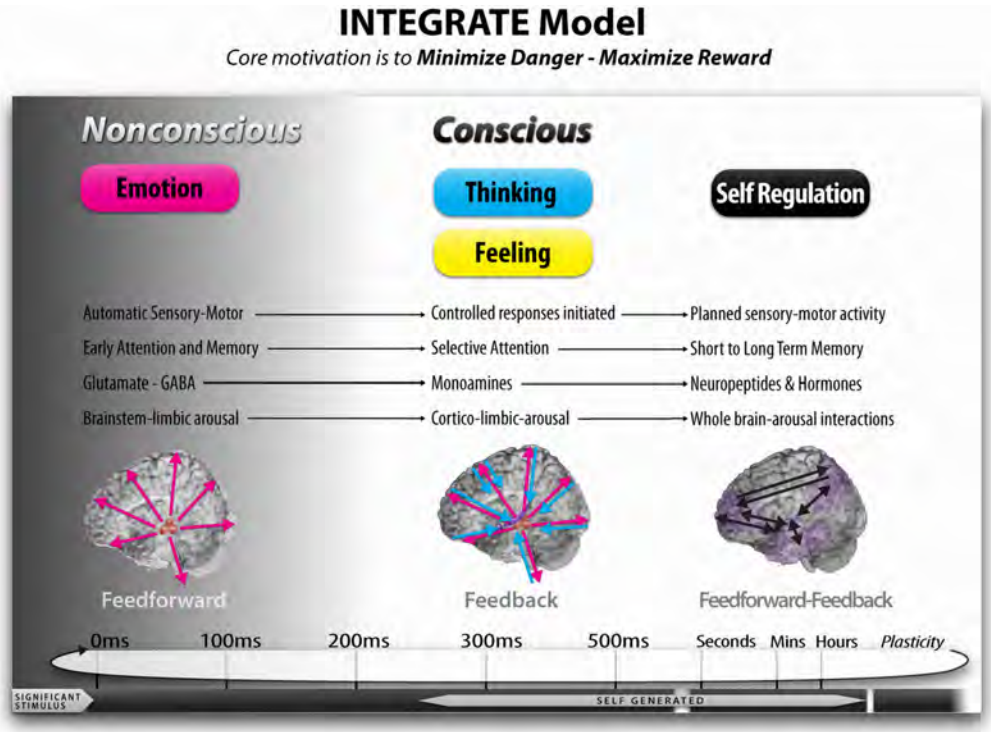


Fig. 1. A visual summary of the INTEGRATE model of brain organization. In this model, the motivation to minimize danger-maximize reward is the key organizing principle of self adaption. This motivation drives emotion, thinking and self regulation along a continuum of time and associated mode of brain 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. These emotional action tendencies are triggered by low level sensory input (sensory store), that elicits automatic sensory-motor repertories, supported by a fast latency feedforward mode of brain and body activity. Rapid-acting neurotransmitters (GABA-Glutamate) are preferentially involved at this early time scale. At longer-time scales (200 ms to seconds) the capacity for "Thinking" and "Feeling" emerges with feedback from brain and body activity, and conscious awareness of this feedback. Thinking supports the initiation of voluntary actions and selective attention, which is necessary to transfer significant information to longer-term memory. Brain-body feedback occurs via reentrant connections from higher cortical brain areas, horizontal connections within brain areas, and mutually interacting brain-body arousal systems. Brain chemicals that have a key role in modulating thinking and feeling are "monoamines"; e.g., dopamine, serotonin and noradrenaline. At longer time scales of multiple seconds, minutes and longer, the capacity for self-generated (as well as stimulus-generated) processing emerges. Self regulation is the shaping and adjusting of our emotion, thinking and feeling over time, to achieve more abstract goals to minimize danger-maximize reward that enhance our well-being and adaption to our environment. It is supported by ongoing cycles of feedforward-feedback brain-body interactions, and slower acting brain chemicals, such as neuropeptides and hormones.

dichotomous concepts of the brain (including cognition-emotion, temporal-spatial, nonconscious-conscious and brain-body).

The organizing principle and time scales of "emotion", "thinking" and "self regulation" may be considered as follows.

*Organizing principle*

*The core organizing principle of self adaption which underlies all aspects of brain-body activity and behavior is to "minimize danger and maximize reward". This principle organizes self adaption by determining what is significant to each of us, at each point in time.*

The minimize danger-maximize reward principle organizes information processing along a temporal continuum — from the early action tendencies that define emotion, to "thinking" functions that emerge after several hundred milliseconds, and "self regulation" that occurs over multiple seconds to hours and longer (Fig. 1). Cognition is considered to be an overarching construct that encompasses these different types of processing across the temporal continuum.

Definitions of "emotion", "thinking" and "self regulation" are provided below:

*"Emotion" — 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.*

For example, when walking in a laneway at night, a dark shape appears abruptly just ahead of you, signaling potential danger. Before you are aware of it, direct sensory input from this visual signal has triggered a feedforward sweep of brain activation, heart rate acceleration and repertoire of motor reflexes that define the action tendency of fear, and the readiness to flee.

*"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.*

To continue the example; with brain-body feedback over the next few hundred milliseconds you identify the dark shape as a person and your feeling as "scared". The context — the person is moving towards you — confirms your perception of danger. You reinforce the tendency to flee, and run until you are out of the laneway and in a busy, well lit street.

*"Self Regulation" — The modulation of emotion, thinking, and feeling to minimize danger-maximize reward over time. Self regulation is inextricably linked to our well-being and adaptation.*

In the above example, the outcome of the experience of walking in the laneway will contribute to our self regulation, such that we minimize our feelings of being scared by avoiding such situations in the future. We may plan so that we do not walk in similar environments at night.

Emotion, Thinking and Self Regulation, and the associated time scales, are considered in more detail in the following sections.

*Emotion — Action tendencies: <200 ms*

In the INTEGRATE model, the action tendencies that define emotion may be triggered automatically within 200 ms post-stimulus (Fig. 1). These action tendencies are triggered by stimuli that are significant because they signal potential danger or reward. At these early time scales, significant stimuli include low level cues that have evolved as innate signals of potential danger-reward, or stimuli that are so highly conditioned that they contain the same significance as innate signals. The properties of these stimuli are sufficiently significant to trigger emotional action tendencies without the need to be consciously aware of them [18, 24, 56].

This view of emotion draws on an evolutionary context, in which action tendencies have evolved as adaptive patterns for survival [13], and do not rely on *subjective* emotional experience or feeling. Darwin argued that emotions are shaped to maximize adaptation. Similar concepts have been proposed in regard to "primary emotion" [11] and "Utilitarian emotion" [59], and the view that humans and other animals share emotions that represent innate tendencies [48].

Emotions and associated action tendencies relevant to minimizing danger-maximizing reward have been grouped into six basic categories: fear, anger, disgust, surprise, sadness and happiness. These action tendencies ready us for dealing with potential danger (for instance, fear for flight, anger for fight, and disgust for withdrawal from contaminants), or for optimizing reward (happiness for facilitating social engagement and sadness for withdrawal and eliciting comfort to reduce distress). In some theories, these basic emotions are referred to by synonymous names; for instance, "anxiety" (fear), "rage" (anger) and "joy" (happiness) [e.g., 34, 51]. Others have proposed a finer-grained differentiation [e.g., 65], or the essential division of "avoidance" versus "approach" tendencies [14, 40]. Much of the research to date has focused on the *feeling* or *expression* of these emotions, and the presumption that evaluation of emotion is needed for action tendencies to proceed. Yet, human adaption clearly depends on the capacity for rapid reactions, and accumulating evidence shows that action tendencies may be triggered automatically and without conscious awareness [81 for review]. The INTEGRATE model explicitly differentiates automatic and nonconscious action tendencies (emotions) from their conscious experience (feelings).

*Autosomatic sensori-motor patterns*: At the level of sensory-motor function, the action tendencies defining emotion may be considered automatic sensory-motor repertoires (Fig. 1). This definition is consistent with the common Latin root for both "emotion" and "motivation" (*movere*, meaning "to move") [77]. It also accords with a phylogenic view; in humans, action tendencies are not necessarily immediately enacted, but constitute the preparation of the individual to react in a certain way [45].

*Earliest Attention and Memory*: The low level stimuli that trigger action tendencies of emotion rely on early attention and memory (Fig. 1). These earliest aspects of attention and memory are equivalent to the concept of a "sensory trace" or "iconic storage" first established in psychology models [63]. It refers to a sensory impression that decays around 250 ms after stimulus onset. By contrast, selective attention (associated with working memory or longer-term memory) emerges at longer time scales, and involve conscious awareness (Fig. 1).

The properties of low-level cues that define their significance as signals of potential danger include abrupt changes that have high intensity (arousability) and unexpectedness ("mismatch"). For instance, a sudden movement or sound may trigger a fear action tendency.[a] Nociceptive stimuli such as pain signals may also trigger a fear or anger action tendency; and bitter or intensely sour tastes, a disgust tendency. Signals of potential reward are also intense, but are "matches" in that they have symmetry or flow rather than abruptness and unexpectedness. These signals include beneceptive stimuli, such as stimulation from sugars or warm touch. In the INTEGRATE Model, these properties are collectively considered "significance primitives" [77].

Highly conditioned stimuli may trigger action tendencies of emotion in the same way that these innate significance primitives would (for instance, stimuli associated with an extreme trauma). Spiders and snakes have also been considered highly conditioned such that they trigger automatic tendencies, although there is also evidence that they have innate significance, related to their unexpectedness [46]. [See 81 for further review, and 19 for detailed hypotheses on evolutionary origins.]

Facial expressions of emotion are the most commonly cited stimuli in regard to the six emotion categories. Indeed, we rely most on the signals communicated from the facial expressions of others to understand our environment [18, 81]. Facial expressions of emotion signal sources of potential danger and reward.[b] These signals rely on equivalent "significance primitives"; for instance, the contrast from the whites of the widened eyes and change in angle of the eyebrow in expressions of fear, versus the distinctive shape of the mouth in expressions of happiness [62, 73]. They have been found to trigger associated action tendencies in the viewer, reflected in distinctive patterns of brain and body activation [81 for review]. The role of expressions of emotion in signaling potential danger-reward is distinct from the *feeling* of emotion they may generate in the viewer, or in the individual communicating the expression.

[a]The emotion of surprise may also be considered to contain the fundamental property of unexpectedness that characterizes fear. Evidence suggest that face stimuli *per se* are distinctive because we can recognize them within the feedforward sweep [47, 66, 67].

[b]Studies of "expressed emotion" also consider facial expressions as signals of the emotion that the individual expressing them is feeling. In the INTEGRATE Model, feeling emerges at a slightly longer time scale (200 ms to seconds) than emotion processing, since it relies on feedback from brain and body arousal. This time scale parallels that for thinking.

*Feedforward brainstem-limbic arousal*: The visual system is an exemplar of how feedforward neural activity supports automatic emotions in the absence of awareness.

The feedforward "sweep" (fast feedforward neural connections completed within 100–150 ms) relies on subcortical sensory input, via brainstem superior colliculus (SC) and pulvinar of the thalamus. Brainstem sensory nuclei such as the SC have been found to respond to low-level input within 40 ms. The feedforward sweep is identified with *nonconscious* processing, while conscious awareness relies on feedback that takes longer to occur.

For cues of danger, this rapid pathway relays signals directly to the amygdala, supporting automatic emotion processing of these stimuli [7, 43]. Seminal fear-conditioning work of Le Doux [41] provided evidence for a concomitant short latency pathway to amygdala for auditory cues of danger.

A corresponding short latency SC pathway implicating automatic reward processing has been identified [10]. In this pathway the SC is crucial to both the activation of dopamine neurons in the ventral midbrain by visual stimuli, and for direct relay of activation to the substantia nigra [10]. The means by which reward signals might be distinguished from unexpected signals of danger within the feedforward sweep has not yet been determined.

Structures engaged in the feedforward sweep also provide rapid and direct input to innervate extrastriate and higher cortical areas — before more detailed input from the slower pathway relying on primary visual cortex and lateral geniculate nucleus has arrived [54]. Direct brainstem innervation of cortical areas such as anterior cingulate may involve the ascending arousal system which, in other lines of work, has been implicated in automatic orienting to significant stimuli [32].

Action tendencies in emotion processing are also expressed in automatic changes in body arousal [81] (Fig. 1). For instance, heart rate acceleration is characteristic of fear-related action tendencies to "flee". We have found that nonconscious signals of fear elicit faster rise time and enhanced skin conductance responses, relative to neutral, and consistent with sympathetically-mediated action tendencies [84, 85]. These findings accord with physiological theories of orienting, which include constructs of defensive orienting to unexpected threat-related stimuli, and associated "fight or flight" systems [27, 52, 53]. They also accord with Damasio's [12] "somatic marker hypothesis" in which arousal may have an automatic, nonconscious influence on decision making to avoid aversive outcomes and maximize positive ones.

*Fast neurotransmitters (Glutamate-GABA)*: The INTEGRATE Model proposes that, at the early time scale of emotion processing, there is preferential involvement of neurotransmitters with fast synaptic transmission such as GABA and glutamate [23] (Fig. 1). As a specific example, both glutamate and GABA transmissions in the amygdala are involved in startle electromyogram (EMG) responses [61]. Preferential involvement is emphasized, given that these neurotransmitters are the basis of neural activity at all time scales.

*"Emotion" and nonconscious perception*: Analysis of neuronal activation in the visual system shows that it is organized according to temporal pathways that do not necessarily correspond to its hierarchical anatomical organization. These pathways provide a structure for understanding how emotional action tendencies can occur in the absence of conscious awareness, via the "feedforward sweep". By contrast, feedback pathways (re-entrant connections from higher cortical areas, as well as lateral within-area connections) take at least a further 100–150 ms to complete, and ongoing feedforward-feedback interactions occur across increasingly long time scales) [38]. Feedback connections are considered further under the following section on "thinking".

*"Thinking": 200 ms to seconds*

At longer time scales of 200 ms to seconds, brain-body feedback supports the emergence of conscious awareness and the capacity for thinking (Fig. 1). The term "feedback" is used to refer to both re-entrant feedback from higher cortical areas and horizontal connections within areas. At these time scales, feedback also allows for the experience (or "feeling") of the emotions triggered at earlier time scales (Fig. 1). This time scale does not imply that thinking *only* occurs within 200 ms to seconds, but that this is the scale at which the capacity to think emerges.

Thinking can provide the context for stimuli that have triggered emotional action tendencies at the earlier time scale. Similarly, feelings (such as the feeling of being scared in the above example) may emerge with brain-body feedback and awareness about mobilization of action tendencies from earlier emotions.

"Thinking" and "feeling" may also occur for stimuli or tasks that have not necessarily triggered an earlier emotional action tendency. For instance, memories of an event associated previously with emotional action tendencies may trigger the associated feeling via slower re-entrant connections. This process is akin to Damasio's [12] concept of "as if" loops that generate emotions "as if" the original stimulus is present. Newly encountered stimuli that do not contain significance primitives will require "thinking" to be processed further. In experimental research, "significance" is often defined according to the task at hand, in order to specifically study the "thinking" processes of selective attention, working memory and related contextual functions.

Converging lines of evidence indicate that feedback connections occur from around 200 ms post-stimulus. That is, following the feedforward sweep at 100–150 ms, feedback connections take approximately a further 100–150 ms to unfold. Edelman [15] used the term "re-entrant" connections to refer to these feedback connections, and their role in supporting conscious processing. While neurons in particular brain regions can support simple detection of stimulus significance at the early time scale of emotion processing, ongoing cycles of recurrent feedback allow these same regions to contribute to increasingly detailed and consciously controlled processing of information over progressively longer time scales.

*Controlled Responses initiated*: "Thinking" and "Feeling" are associated with the initiation of controlled actions (Fig. 1), which are necessary to voluntary decisions and behaviors. In physiological models, they have been associated with controlled orienting to significant changes in the environment [27].

*Selective Attention*: Brain-body feedback emerging from around 200 ms onwards supports the selective processing of significant stimuli, referred to by the umbrella term "selective attention" in the INTEGRATE Model (Fig. 1). Selective attention, reliant on recurrent feedback, allows features relevant to the significance of a stimulus to be enhanced [38]. This may involve the preferential processing of one source of input whilst being able to ignore another. Selective attention also involves contextual processes, such as the comparison of new information with stored information. These aspects of selective attention rely on working memory, i.e., the capacity to hold information "online", and to update memory with new and significant input. Selective attention facilitates the transfer of significant information from sensory storage to short and long term memory, which operate over the longer time scales of seconds to minutes and longer (Fig. 1; further details in the following section).

The significance of a stimulus (or other source of information) is relevant to how these aspects of selective attention and working memory are organized. In psychological models, working memory is part of the short term memory (STM) store that can emerge after a few hundred milliseconds and last up to about 20 seconds [4]. Its capacity is often called "memory span"; on average about $7 \pm 2$ "chunks" of information. The concept of "chunking" can increase this capacity, and is relevant to our core principle of significance (minimizing danger-maximizing reward). For instance, in our above example, the loud noise is given priority in processing systems (due to fear), and working memory allows us to integrate this sensory input with stored knowledge about the stimulus and prior associations with it. The effect of significance can make our memory span capacity skyrocket. "Chunks" of incoming information must be bound in an organized manner. A candidate mechanism, receiving much attention, is neural synchrony [42]. For example, the phase synchrony (rather than firing rate) of Theta activity across different neural networks may be necessary for binding together different sources of stimulation into a coherent whole.

*Cortico-limbic-arousal feedback*: Studies of brain activity have shown that neuronal systems are able to hold this information without the need for external input, consistent with the operation of recurrent feedback. The emergence of context processing and working memory has been associated with a 300–600 ms time scale [e.g., 8]. The time frame of slow wave EEG, such as the Theta frequency band (approx. 4–7 Hz), is consistent with the time scale of "thinking" (i.e., oscillating every 250–300 ms). Increases in working memory load have been associated with increased Theta power [36]. The time scale of thinking and feeling implicates both sensory cortical networks and higher order cortical networks such as the lateral and medial prefrontal cortices and parietal cortices. The hippocampus and its connections with the

lateral prefrontal cortex is preferentially involved in supporting contextual functions, and updating of working memory for transfer to short and then long term storage.

Feedback from body arousal also shows effects on brain function from around 200 ms post-stimulus. Consciously perceived fear signals elicit even greater skin conductance responses (SCRs) than nonconscious fear, associated with changes in electrical brain activity around 200–250 ms post-stimulus [85]. SCRs to other significant stimuli, such as unexpected high-pitched tones in an oddball task, are also correlated with brain activity in this timeframe [44]. These correlations accord with Adolph's [1] model in which emotional reactions involving the body are elicited around 200 ms post-stimulus. In Damasio's [12] "somatic marker hypothesis" arousal feedback to amygdala and medial prefrontal circuitry is also seen to modulate conscious decisions to minimize negative and maximize positive outcomes. Behavioral studies have found that we are able to report on our "feeling" of emotion from around 500 ms onwards [75].

*Monoamines*: In terms of neurochemistry, functions of thinking and feeling are supported by modulation of monoamines, such as serotonin, dopamine and noradrenalin (Fig. 1.)

*"Thinking", "Feeling" and Conscious Awareness*: Understanding the construct of "consciousness" remains a challenge for neuroscience. Here, we have defined "conscious awareness" experimentally as the threshold for awareness of sensory stimulation. Under this definition, awareness for significant stimuli is seen to depend critically on brain-body feedback. The prevailing view is that a subcortical/cortical division distinguishes nonconscious from conscious sensory processing. In the INTEGRATE Model, the crucial differentiator is *mode of connectivity rather than anatomical region*, with feedforward connections being sufficient for nonconscious emotion, and feedback connections being necessary for detailed and conscious evaluation. Evidence from functional MRI with connectivity analysis is consistent with this distinction. Signals of danger presented below awareness elicited a predominance of positive connectivity between brainstem, pulvinar and amygdala, and in the distributed projections to anterior cingulate-medial prefrontal and extrastriate cortices (indicating a feedforward mode). By contrast, conscious awareness of the same stimuli was supported by a predominance of negative connections between these regions, as well as a greater presence of cortical-cortical negative connections (indicating a feedback mode) [79]. In functional brain mapping analyses, there was substantial overlap between these conditions in regions of brain activation. The experimental protocol used backward masking to prevent sensory awareness, consistent with the view that the mask interrupts the capacity for recurrent feedback from higher cortical areas [38].

Some researchers have proposed that neural synchrony is reliant on recurrent activity, and may be a necessary condition for conscious awareness of a stimulus. Notably, however, "spontaneous" synchrony has also been observed in response to the intensity of a stimulus [68], suggesting it may occur with early process of low

level significance primitives. This area requires investigation, including the question of whether synchrony in different frequency bands (Gamma, Beta, Alpha, Theta) is associated with time scales of emotion, thinking and self regulation.

*Self Regulation: Seconds and longer*

At time scales of seconds or longer, self-generated processing becomes possible, in addition to processing triggered by stimuli in the external or internal environment (Fig. 1).

Self regulation is about reinforcing our emotions, thinking and feeling — and associated behavioral responses — that maximize reward-related outcome over time, and minimizing those that are ill-matched to our needs and likely to increase sources of danger. In other words, we regulate ourselves to better serve our adaptive goals of minimizing danger-maximizing reward over time.

*Planned Sensory-motor activity*: The construct of self regulation has been articulated in several disciplines, including psychology (as self control and emotion regulation) [e.g., 30] and medicine (as homeostasis). The concept of "conation" has also been used in relation to self regulation [77]. In common, these concepts highlight the "self" or the "will" as the source of processing, rather than a stimulus. At the level of sensory-motor function, there concepts accord with planned activity that can be monitored and modulated.

In this sense, self regulation relies on self awareness, a capacity not thought to be present in other species. At the most abstract level, it provides our sense of self. Over these time scales, our adaptive goals may represent more abstract formulations of minimizing danger-maximizing reward. For instance, when asked to give a public speech, we may try to think of positive associations, and how well we have done in previous speeches, so we minimize our feeling of being scared, and the risk that we expose ourselves to a threat. An individual's sense of self may be reinforced by the degree to which outcomes reinforce or are discrepant from the goals set to minimize danger-maximize reward.

*Short to Long-term memory*: The ongoing outcomes of self regulation will be crucial in organizing our memory storage, and how memories are linked over time. Short term memory (STM) operates over a few to about 20 seconds, and long term memory (LTM) over hours to a lifetime (Fig. 1). It is not simply the case that the longer a piece of information stays in STM then the more likely it is to go into LTM. Instead, the more significant a stimulus or event is then the greater likelihood it is retained in the type of LTM known as "semantic memory". This is why we remember events relevant to our self adaption much more readily than otherwise "neutral" ones, even when loss of factual memory (e.g., due to dementia) occurs.

Another type of LTM, "episodic memory", is crucial to the capacity for linking our own experiences over time, from past events to imagined future ones. The full capacity for this type of LTM is developed only in adolescence (around 14 years old). Self awareness shows a corresponding developmental trajectory [39, 45]. When fully developed it allows us to reflect on our own thoughts and feelings and make

attributions about others" thoughts and feelings [39] — a construct known also known as "autonetic consciousness" and "theory of mind".

While LTM stores apparently limitless information (compared to the capacity constraints of STM), it has been argued that STM and LTM are not separate systems, but rather a unitary phenomenon that spans seconds to years [5]. The concept of a memory continuum is relevant to the wide time scale of self regulation in the INTEGRATE Model (Fig. 1).

*Whole brain-arousal interactions*: Self regulation is supported by ongoing interactions between brain-body feedback and feedforward connections (Fig. 1). These ongoing cycles allow regions implicated at earlier time scales to also be involved in self regulation. The concept of cycles of feedback overlaps partly with the notion of "top-down" influences. LTM in itself has been considered a "top-down" influence on how we bring our prior experiences to bear on the perception of significance in the environment.

In the INTEGRATE Model, time (allowing for increasing numbers of feedback cycles) and mode of connectivity distinguish the involvement of the same regions in different functions. For instance, the medial prefrontal cortex is implicated in automatic emotional action tendencies (via direct feedforward innervation) and in emotion regulation over seconds and longer (arguably via ongoing cycles of feedback re-entrants to both subcortical and other cortical regions). Damasio [12] has implicated the medial prefrontal region in the regulation of social and interpersonal behaviors, as well as more automatic emotion processing.

A mechanism compatible with cycles of feedforward-feedback neural activity is the "mirror neuron" system, thought to underlie both the perception of goal-directed action, and imitation learning in primates. This (or similar) mechanism may underlie the regulation of social cognitions by enabling an understanding of the actions of others, and the regulation of oneself in relation to that understanding [29, 45].

Several measures have been associated with self regulation. For instance, asymmetry of neural activation (assessed by the EEG) has been implicated in regulating the balance of negative versus positive emotion [14]. In terms of the body, heart rate variability is considered an index of self regulation, in terms of the organization of physiological feedback and its integration with brain activity, in order to increase processing of significant information when required, and inhibit it when not, in relation to changing environmental demands [64].

We have identified behavioral dimensions of "social cognition" that capture the construct of self regulation as it relies on self awareness and feedback about our brain and body activity, negativity bias (the tendency to focus on negative versus positive events in the environment), emotional resilience (the capacity for resisting negative stressors to maximize our confidence and self-efficacy) and social skills (the capacity for regulating oneself in connection to others, related to traits of extraversion and empathy) [55, 89].

*Neuropeptides and Hormones*: Relevant to the longer time scales of self regulation are neuropeptides and hormones (Fig. 1). The faster acting neurotransmitters

(such as the monoamines) also continue to modulate information processing over these time scales, associated with brain-body feedback. Indeed, these faster-acting neurotransmitters coexist with specific neuropeptide classes. Notably, neuropeptides have a regulatory role associated with specific aspects of information processing and behavior, and which is relevant to minimizing danger-maximizing reward. When emotional reactions and thinking are negative, they produce a depression of the immune system, and when they are positive they enhance the immune system. This role is different from that of the earlier acting neurotransmitters. As an example, oxytocin and vasopressin have striking and specific effects on enhancing reward-related social behaviors, including maternal behavior and pair bonding. Some neuropeptides also express hormones. For instance, neuropeptide Y (NPY) and alpha-melanocyte stimulating hormone ($\alpha$-MSH) have been found to interact in the regulation of fear-related anxiety [37].

*Plasticity*: In the INTEGRATE Model, the time scale of self regulation spans seconds to the lifespan, which is clearly an extensive period of time. This long time scale is not intended to imply that identical functions operate across this scale, but that there is an essential commonality in self regulatory functions over time. In finer-grained consideration of this time scale, we might differentiate functions that emerge over seconds (such as short term memory) from those that operate over days or longer (such as regulation of negativity bias and mood).

The role of plasticity must also be considered (Fig. 1). With ongoing outcomes from emotion, thinking and self regulation, there will be adaptive changes in the brain, termed "plasticity". Over the lifespan, some self regulatory functions may become "routinized" and have similar automaticity to emotions, even though they may still rely on feedback and awareness. For instance, if we have learnt from our experience which signals are the most significant (in terms of danger-reward) and which may be "false alarms", the resulting plasticity may bring a relatively more adaptive and "routinized" way of regulating reactions to such stimuli.

### *Implications for mental health*

The concepts of Emotion, Thinking and Self Regulation are considered here mainly in relation to normative adaption. However, they are also seen as the framework for understanding how disorders of mental health may develop from alterations in Emotion, Thinking and Self Regulation. As an example, anxiety may be considered as reflecting an excessive action tendency of fear, with a heightened perception of potential signals of threat in the environment. What makes it the experience of anxiety in humans is the effect on Thinking (increased selective attention to sources of threat), feeling (the awareness of brain-body changes associated with the excessive fear, such as heart rate pounding, muscle tension) and Self Regulation (the memory of these experiences will reinforce expectation of threat-related rather than reward-related outcomes).

### 1.2. *Age, genetic variation and the INTEGRATE model*

The INTEGRATE model offers a framework for examining the contribution of dispositional factors such as genetic variants and age to the processes of emotion, thinking and self regulation. Much attention has been given to the role of genetic variants known to modulate monoamines such as serotonin, dopamine and noradrenaline (e.g., SCL6A4, MAOA, COMT, DRD4) as well as overall neural plasticity and resilience (e.g., BDNF) in effecting functions of emotion, thinking or self regulation. For instance, the insertion/deletion polymorphism in the promoter of the serotonin transporter gene SCL6A4 (5HTT-LPR) has been associated with fear processing, and anxiety and depressed mood, reflecting the respective time scales of "emotion" and "self regulation" in the INTEGRATE model. The 5HTT-LPR "short" allele has been related to excessive startle responses and poorer connectivity in amygdala-medial prefrontal networks [33].

The variable number of tandem repeat VNTR polymorphism in MAOA, that impacts monoamine metabolism (in particular, dopamine and noradrenaline) [70], and has also been implicated in "emotion" and "self regulation". Low activity MAOA variants have been associated with altered ERPs elicited by facial emotion within the first 200 ms, and with antisocial trait aspects of temperament [83].

COMT is involved in catabolism of prefrontal dopamine. The $Val^{108/158}$Met polymorphism in this gene has been implicated in cognitive functions on the "thinking" time scale, such as sustained attention and working memory functions [16]. The Met allele, on the other hand, has been linked with relatively poorer emotion recognition [72].

The VNTR in the *DRD4* gene, which is also involved in neuromodulation of dopamine, has been implicated in "thinking" and "self regulation" processes, but with opposing effects. Carriers of the 7-repeat allele (DRD4-7-repeat) show reduced activity in a selective attention task, reflected in ERPs elicited around 300 ms post-stimulus, relative to DRD-2-repeat and DRD-5-repeat carriers [71]. On the other hand, DRD4-7-repeat is associated with relatively superior impulsivity assessed by novelty seeking, when combined with exposure to a hostile child-rearing environment [35].

Polymorphisms implicated in neural plasticity have also been found to modulate "thinking" and "self regulation". The Met allele of the BDNF $Val^{66}$Met polymorphism, implicated in poorer neural plasticity, has been linked to a relative reduction in declarative memory and a slower P300 ERP during selective processing [17, 60]. It has also been found to contribute to modulation of negative mood via effects on brain function [21, 22].

It has been argued that genetic mechanisms should not be expected to code for domain-specific functions, but for the predisposition of neural systems to undertake certain cognitive and emotional tasks [58]. The ongoing impact on brain and behavior arises from a subtle interplay between genetic predisposition and experience throughout the lifespan, rather than being solely prescribed by genetic variations.

The role of development, maturation and aging in shaping emotion, thinking and self regulation has typically not been addressed in studies of genetic variants and brain-behavior measures. In this study, we examined participants spanning childhood through to adulthood and older age, as a means of capturing the effects of development, maturation and aging.

One of the most striking features of mental disorders, such as anxiety, depression, psychosis and attention-deficit disorders, is their variation in age of onset, and their progression across the lifespan [58, 90]. This variation suggests that brain-body changes occurring with normal development, and aging may act as additional points of vulnerability which contribute to their phenotypic expression. The interaction of genetic polymorphisms with changes in brain and behavior across age may contribute to the vulnerability for these disorders at specific phases of the lifespan.

The aim of this study was to apply the INTEGRATE Model to examine the impact of age and genetic variants (COMT, MAOA, BDNF, 5HTT-LPR and DRD4), and their interaction, on emotion, thinking and self regulatory functions.

## 2. Methods

### 2.1. *Subjects*

The participants and data acquisition for this study involved an international consortium linked to the Brain Resource International Database (BRID; www.brainresource.com; [24,25]), and spanning Australasian, European and US sites.

One thousand and eight healthy subjects (mean age = 31.57, SD = 18.68, range = 6–84; 503 females and 505 age-matched males) were recruited. 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). These criteria were assessed with a web-based questionnaire, including items from the SPHERES, AUDIT and Fagerstrom scales.

Following our previous work which established norms of the cognitive tests [20], subjects were recruited to equitably represent the distribution of peak periods of change on these tests (with equivalent numbers of males/females, ranging from 49–51% in each sex in each age band): 6–9 yrs ($n = 87$), 10–13 ($n = 121$), 14–19 ($n = 121$), 20–29 ($n = 182$), 30–39 ($n = 139$), 40 to 49 ($n = 130$), 50–59 ($n = 112$), 60–84 ($n = 108$). Estimated IQ, using a spot-the-word test, was equivalent across these age bands. These participants were genotyped and completed cognitive and brain function assessments.

A large subset of these participants ($n = 221$) also underwent MRI assessment of brain structure. This subset did not differ in demographic distribution from the total group. A larger cohort was not possible due to the scheduling constraints of the MRI facility, but there was no systematic effect in relation to which participants were unable to complete this component.

Subjects gave written informed consent, in accordance with medical research council guidelines.

### 2.2. *Summary of measures*

Table 1 provides a summary of the measures used in this study in relation to the Emotion, Thinking and Self Regulation time scales of the INTEGRATE Model.

Each of these measures is considered in turn below:

### 2.3. *Cognition*

*"Thinking" time scale*

Tests of general cognition were part of a fully computerized and standardized battery; "IntegNeuro" [24, 25]. This battery is presented on a touch-screen computer and does not rely on keyboard or computer skills, thereby making it readily applicable to subjects across a wide range of ages. The IntegNeuro test battery was administered in a sound-attenuated testing room, with participants seated in front of the touch-screen computer (NEC MultiSync LCD 1530V). Standardized task instructions were presented visually on the screen and using concurrent audio files (via headphones). Non-verbal responses (reaction time and accuracy) were recorded via the touch-screen computer and verbal responses were recorded via a microphone and recording system attached to the headphones. The test battery has established psychometric properties, including validation against traditional paper and pencil tests tapping equivalent domains, test-retest reliability and consistency across cultures [49, 50, 88].

Individual tests of general cognition making up the IntegNeuro battery, and which reflect the "thinking" time scale in the INTEGRATE Model, are summarized in Table 2. These tests form seven domains of general cognition, established using principal components analysis (PCA), with oblimin (delta = 0) rotation [55]. We focused on standardized domain scores defined as follows:

(1) Sustained Attention: reaction time and errors for the $n$-back continuous performance test of sustained attention.
(2) Sensori-motor Response Speed: the average pause between taps for the dominant and non-dominant hands.
(3) Working Memory Capacity: forwards and reverse digit span scores.
(4) Information Processing Efficiency: visual-verbal interference score for Parts I and II, switching of attention duration for Parts I and II, and choice reaction time (also known as Information Processing Speed).
(5) Verbal Processing: number of words generated on the tests of verbal (FAS) and semantic (animal category) fluency.
(6) Executive Function: maze test completion time and number of overrun errors, and span of visual memory.

Table 1. Summary of measures used in this study according to the temporal continuum of processing in the INTEGRATE Model.

| Organizing Principle | Disposition | "Emotion" 0–200 ms | "Thinking" 200-seconds | "Self Regulation" Seconds+ to minutes to days+ |
|---|---|---|---|---|
| Minimize Danger/ Maximize Reward | *Genetic variants:* COMT $Val^{108/158}Met$ MAOA High & Low DRD4 2/4 & 7 repeat BDNF $Val^{166}Met$ | | *Cognitive-behavioral measures* Working Memory Capacity Sustained Attention Verbal Processing Sensori-motor Response Speed Verbal Memory Executive Function Info. Processing Efficiency | Negativity Bias Emotional Resilience Social Skills |
| | | Fearful face VPP ERP "Automatic" NoGo N200 ERP | *Activation task ERPs** Oddball "Selective Attention" P300 ERP Sustained Attention P300 Working Memory P450 ERP | |
| | | Alpha and Beta power | *EEG* Theta and Delta power | |
| | | *Brain systems* Subcortical feedforward | *Brain systems* Cortical–subcortical feedback | *Brain systems* Cortical–subcortical Feedforward Feedback interactions |

*Note: For completeness, secondary analyses examined the early "Emotion" time scale for ERPs listed in the "Thinking" time scale, and vice versa to determine that age and genetic effects were associated primarily with temporal phase and mode of processing rather than a specific paradigm *per se*.

Table 2. The individual tests of "thinking" (general cognition) making up the "IntegNeuro" battery.

| Test[a] | Description |
|---|---|
| *Verbal Interference* | Colored words with incongruent color-word combinations are presented, and name (Part I) and color (Part II) of each word are identified. Assesses aspects of inhibition and interference corresponding to those indexed by the Stroop test. |
| *Switching of Attention* | In Part I, 25 digits are identified in ascending numerical sequence (i.e., $1, 2, 3 \ldots$), and in Part II, 13 digits (1–13) and 12 letters (A–L) in ascending sequence of alternating digits and letters (i.e., 1 A 2 B 3 C. . . ). Assesses constructs equivalent to those assessed by Trails Making A and B. |
| *Choice Reaction Time* | One of four target circles is illuminated pseudorandomly in 20 trials, and each illuminated circle is touched as quickly as possible. |
| *Verbal Learning & Recall* | Trials 1–4 assess learning rate and immediate recall for a 12-word list, Trial 5 is new "distractor" words, Trial 6 assesses "short delay recall" and Trial 7, "long delay recall" (after 20 min). "Recognition memory" is also assessed. Lists are matched on word length, concreteness and frequency, and semantic or phonemic similarities are excluded. This test assesses similar constructs to those evaluated by the Rey Auditory Verbal Learning and Memory test. |
| *Digit Span* | The order of digit series (e.g., $4, 2, 7$ etc.), each 500 ms, in both forward and reverse order conditions, is recalled using a numeric keypad. Number of digits is gradually increased from 3 to 9. |
| *Span of Visual Memory* | Randomly arranged squares are highlighted sequentially on each trial, in both forward and reverse conditions. Subjects repeat this order. It is a computerized variant assessing similar aspects of memory to the Corsi blocks. |
| *Sustained Attention* | An N-back continuous performance test of sustained attention. Subjects identify 85 "targets" (consecutive letters B, C, D or G) within a pseudorandom series of 125 letters of 200 ms, ISI 2.5 secs. Speed and accuracy are stressed equally. |
| *Tapping* | Subjects are required to tap a circle with the index finger of their dominant and then their non-dominant hand, as fast as possible, for 60 seconds each. |
| *Letter Fluency* | Subjects generate words that began with the letters F, A and S, recorded via "wav" files, allowing 60 seconds for each letter. Proper nouns are not allowed. |
| *Semantic Fluency* | Subjects generate animal names in a 60 second period, recorded via "wav" files. |
| *Maze* | 24 consecutive correct moves are required to identify a hidden path within a $8 \times 8$ "maze". Incorrect moves elicit a tone and red cross, and correct moves a different tone and green tick. Test ends with two error-free completions (or time-out after 7 mins). A computerized variation assessing similar constructs to those assessed by the Austin Maze. |

[a]Since this study, a test of explicit emotion identification and implicit face recognition is also now available [86].

(7) Verbal Memory: immediate recall, delayed recall and memory recognition on the verbal recall test.

*"Self Regulation" time scale*

Social cognitive functions include the regulation and attribution of emotional and interpersonal functions. These social cognitive constructs are assessed using the Brain Resource Inventory of Social Cognitions (BRISC), which has been established using factor analysis of measures of emotional intelligence, negative attributional traits and temperamental traits [55, 89]. A Principal Component Analysis (PCA) using an obliminal (delta = 0) rotation was again employed. The three domains of social cognitive function are defined as follows:

(1) Negativity Bias: The tendency to see yourself and your world as negative. Associated with sensitivity to stress and emotional stability. Scores are inverted such that low scores indicate an excessive negativity bias, and high scores a positivity bias.
(2) Emotional Resilience: Capacity for coping with life and feeling confident in yourself and your opinions. Related to self-esteem, self-efficacy and self-assurance.
(3) Social Skills: Capacity for building and maintaining relationships, and understanding other people. Associated with extraversion and empathy.

### 2.4. *ERPs*

*"Emotion" time scale*

Subjects were asked to refrain from smoking and caffeine consumption for two hours prior to assessment of event-related potentials (ERPs). EEG data were recorded continuously from 26 scalp sites with a 500 Hz sampling rate, using a NuAmps and International 10–20 electrode system, with a Quikcap and Ag/AgCl electrodes. A virtual ground was used, with offline referencing to linked mastoids. For each activation task, peak ERP components were identified within defined latency windows, validated by visual inspection across individual subjects for each recording site. The focal sites of interest for this study were the frontal and parietal sites, as representative of each task.

*Facial emotion ERPs.* We recorded EEG data during the previously established Facial Expressions of Emotions for Brain Activation task (FEEBA) [82, 87]. Grey scale 3-D evoked facial expression stimuli (depicting fear, anger, disgust, sadness, happiness, and neutrality) were selected from a standardized set of stimuli [31]. A total of 96 stimuli (8 different individuals depicting each expression) were presented pseudorandomly for 500 ms, with inter-stimulus interval (ISI) 767 ms. The focal ERP of interest was the Vertex Positive Potential (VPP, peaking around 170 ms post-stimulus), quantified for fear, happy and neutral face stimuli. We have found the VPP to be modulated by emotion, feasibly via automatic processes [82, 87].

*NoGo ERPs:* In a "Go NoGo" design, subjects were repeatedly presented with green colored stimuli (the word "press") for 75% of the time, and a red colored stimulus for 25% of the time. They were asked to press the button box as quickly as possible for the green stimuli, and to withhold responses for the red. Speed and accuracy were equally stressed. We quantified the negative going N200 ERP (150–230 ms) for NoGo stimuli, elicited within the time scale of "automatic" error detection established previously [57]. (We also quantified the P300 within 280–450 ms, for secondary analyses, consistent with the "controlled" NoGo positivity previously established [57]).

*"Thinking" time scale*

*Selective Attention ERPs.* Subjects undertook an Auditory Oddball task, comprising a series of high and low tones, at 75 dB and lasting for 50 ms, with an interstimulus interval (ISI) of one second. Rise and fall times of the tones was 5 ms. Subjects were instructed to press buttons with the index finger of each hand in response to "target" tones (presented at 1000 Hz). No response was required to "background" non-target tones (presented at 500 Hz). Speed and accuracy of response were equally stressed in the task instructions. Tones were presented in a quasi-random order, with the only constraint being that two targets cannot appear consecutively. We focused on the primary ERP for this task; the P300 (270–450 ms) elicited by oddball targets. For secondary analyses, we also examined the N100 (80–140 ms) for target ERPs.

*Sustained Attention and Working Memory ERPs.* 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. Subjects 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 sustained attention ERP, P300 (285–450 ms) and the working memory updating P450 (300–550 ms).

### 2.5. *EEG*

For recording of resting condition EEG, participants were asked to relax with eyes closed. The two minutes of EEG recording was divided into adjacent intervals of four seconds. Power spectral analysis was performed on each four second interval using Fast Fourier Transformation (FFT). Using the resulting averaged spectra, power was calculated for four frequency bands, delta (1.5–3.5 Hz), theta (4–7.5 Hz), alpha (8–13 Hz), and beta (14.5–30 Hz). These power data were then square-root transformed to meet the assumptions of a normal distribution.

### 2.6. *Structural MRI*

Structural MRI scans were conducted on a matched subsample of 276 participants including 128 males and 148 females. High resolution structural MRI images were

acquired, using a T1 (MPrage) sequence, in the sagittal plane, with 180 slices, 1 mm cubic voxels, 256 × 256 matrix: TR 9.7, TE 4, TI 200 and flip angle 12. Segmentation and spatial normalization of MRI data were performed using voxel based morphometry (VBM) in SPM2 (http://www.fil.ion.ucl.ac.uk/spm/spm2.html) using customized templates created from 223 individuals in the BRID [28]. Images were spatially normalized by transforming each brain to a standardized stereotactic space of MNI (Montreal Neurological Institute). Images were segmented into grey and white matter and CSF using a cluster analytic method to separate pixels based on intensity differences [9]. A correction was made to preserve quantitative tissue volumes following normalization procedure [3].

Search regions of interest were defined using standardized neuroanatomical masks from the AAL system [69]. Cortical regions included the Medial PreFrontal Cortex (MPFC, ventral and dorsal portions), Lateral PreFrontal Cortex (LPFC, ventral and dorsal portions) and Parietal cortex (inferior and superior portions). Subcortically, the boundaries for the amygdala were defined caudally by the uncus of the parahippocampal gyrus and rostrally, by the hippocampus. Hippocampal grey matter included the hippocampus proper, dentate gyrus and uncus, limited caudally by the parahippocampal ramus of the collateral fissure.

### 2.7. *Genotyping*

DNA was extracted from cheek swab samples by a standard proteinase digestion and chloroform extraction procedure. BDNF $Val^{66}Met$ and COMT $Val^{108/158}Met$ genotyping was performed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis. PCR amplification of participant DNA was undertaken using the following primers: *BDNF*, 5′-TGTATTCCTCCAGCA GAAAGAGAA-3′ and 5′-AAAGAAGCAAACATCCGAGGAC-3′; *COMT*, 5′-TGT CACCAGGGGCGAGGCTCAT-3′ and 5′-CGGCCCTTTTTCCAGGTCTGAC-3′ using standard conditions. BDNF amplicons were digested with the restriction enzyme *Af*lIII, and COMT amplicons were digested with *Nla*III. Digested products were separated by agarose gel electrophoresis. MAOA and DRD4 VNTR genotypes were determined by PCR amplification with fluorescently labeled primers and capillary electrophoresis on the 3730 DNA Analyzer (Applied Biosystems, Foster City, CA). Primers used were: *MAOA*, 5′-ACAGCCTGACCGTGGAGAAG-3′ (labeled with 6-FAM) and 5′-GAACGGACGCTCCATTCGGA-3′; *DRD4*, 5′-GGT CTGCGGTGGAGTCTG-3′ (labeled with 6-FAM) and 5′-GCGACTACGTGGTC TACTCG-3′. The 5HTT-LPR polymorphism was genotyped using the method described by Wilhelm [76]. Genotypes were scored independently by two researchers.

Genotype groups were formed in accordance with previous studies. These groups were: 5HTT-LPR (68% short allele carriers versus 32% LL homozygotes), $COMT^{108/158}$ (43% VV versus 57% MM homozygotes), DRD4 (37% 7-repeat carriers [7/7, 7/4 and 7/2 genotypes] versus 63% 2–4 repeat carriers [2/2, 2/4 and 4/4 genotypes]), MAOA (69% High [3.5, 3.5/4, 4, 4/4] versus 31% Low [3, 3/3] activity) and $BDNF^{66}$ (45% Met carriers versus 55% VV homozygotes).

## 3. Results

### 3.1. *Main effects of age*

Regression analyses were undertaken using both linear and quadratic models to determine the effect of age on each of the measures. Trajectories of age-related change in these measures were each confirmed by contrasts between more homogenous age groups of participants aged 6–14, 25–39 and 50–80 years. The results are organized according to the grouping of measures along Emotion, Thinking and Self Regulation time scales in Fig. 1.

*"Thinking" time scale*

Each domain of general cognition followed an inverted-U shaped trajectory over age, and the contribution of age was substantial (17 to 30%) (Table 3). After an initial improvement from six until the late teens or early twenties, there was a short plateau across the mid twenties to thirties, followed by a decrease in each general cognitive domain which was particularly marked from 50 years onward.

Correspondingly, age predicted a decline in the later ERPs; "Selective Attention" P300 ERP for the oddball task, for the "Sustained Attention" P300 from the working memory task (target stimuli), and the "Working Memory" P450 ERP (non-target stimuli) (Table 4). The age-related decline in these ERP components paralleled the decline in domains of general cognition.

In EEG recordings, age predicted a marked linear decline in slow wave Theta and Delta power, and explained over 40% of the variance in slow-wave activity (Table 6), again paralleling the findings for general cognition and later ERPs.

Table 3. Summary of regression and contrast statistics for the prediction of domains of "thinking" (general cognition) and "self regulation" (social cognition) by age (for corrected alpha level, $p = 0.001$).

| Measure | Age $F$-Value | Age $p$ Value | $R^2$ due to Age | Direction of Effect |
|---|---|---|---|---|
| *"Thinking": Reduction over age* | | | | |
| Working Memory Capacity | 138.61 | $< 0.0001$ | 23.4% | ↓ |
| Sustained Attention | 195.95 | $< 0.0001$ | 30% | ↓ |
| Information Processing Efficiency | 96.17 | $< 0.0001$ | 17.4% | ↓ |
| Executive Function | 125.93 | $< 0.0001$ | 22.7% | ↓ |
| Verbal Processing | 108.44 | $< 0.0001$ | 19% | ↓ |
| Sensori-Motor Response Speed | 59.44 | $< 0.0001$ | 17.6% | ↓ |
| Verbal Memory | 177.73 | $< 0.0001$ | 27.5% | ↓ |
| *"Self Regulation": Preservation or increase over age* | | | | |
| Negativity Bias[a] | 13.74 | $< 0.0001$ | 4% | ↑ |
| Emotional Resilience | 29.91 | $< 0.0001$ | 9% | ↑ |
| Social Skills | 14.81 | $< 0.0001$ | 4.5% | — |

[a]This value is inverted in order that all measures may be interpreted in a consistent direction (i.e., higher scores = better function; lower scores = worse function).

Table 4. Summary of regression and contrast statistics for the prediction of ERPs by age (for corrected alpha level, $p = 0.001$).

| Activation Task ERPs | Age $F$-Value | Age $p$ Value | $R^2$ due to Age | Direction of Effect |
|---|---|---|---|---|
| *Late ERPs reduced over age* | | | | |
| Selective Attention P300[a] | 826.26 (Fz)* | $< 0.0001$ | 45.5% | ↓ |
| | 54.95 (Pz) | | 5.5% | |
| Sustained Attention P300 | 181.81 (Fz) | $< 0.0001$ | 16.4% | ↓ |
| | 55.51 (Pz) | | 5.7% | |
| Working Memory P450 | 221.23 (Fz) | $< 0.0001$ | 33.3% | ↓ |
| | ns (Pz) | | — | |
| *Early ERPs increased over age* | | | | |
| Face VPP | 57.04 (Fz) | $< 0.0001$ | 20.5% | ↑ |
| | 20.77 (Pz) | | 8.6% | |
| Fearful Face VPP | 181.81 (Fz) | $< 0.0001$ | 16.4% | ↑ |
| | 55.51 (Pz) | | 5.7% | |
| Automatic "NoGo" N200[a] | 21.03 (Fz) | $< 0.0001$ | 4.4% | ↑ |
| | 5.74 (Pz)* | 0.02 | 0.6% | |

*A quadratic relationship indicating poorer performance in younger as well as older individuals
[a]Notably, there were corresponding "paradox of aging" effects for the Early and Late ERPs within these tasks (undertaken as part of secondary analyses in the study). For example: for the Oddball Selective Attention task, the early N100 reflecting automatic orienting was increased over age at both Fz and Pz ($p < 0.0001$) sites, consistent with effects for the "Emotion" time scale. By contrast, for the NoGo P300 associated with "controlled" processing, there was a decline over age at Fz (quadratic, $p < 0.0001$) and Pz (linear, $p < 0.0001$), consistent with effects for the "Thinking" time scale.

Brain structure, assessed by MRI, showed consistent linear reductions over age. MR images revealed a linear reduction in cortical grey matter over age, which was most pronounced for frontal and parietal association cortices (Table 5).

### *"Emotion" and "Self Regulation" time scales*

By contrast, negativity bias and emotional resilience domains of social cognition at the time scale of Self Regulation showed the inverse trajectory (Table 3), consistent with a "paradox of aging". Older age was associated with a greater positivity bias (i.e., lower negativity bias) together with an increasing capacity for emotional resilience (Table 3), consistent with better emotional stability. The social skills domain of social cognition was relatively preserved over age (Table 3).

A corresponding "paradox of aging" was revealed for early ERPs elicited by facial emotion and NoGo stimuli. Increasing age predicted an increase in the VPP elicited by face and fearful face stimuli and in the "Automatic" N200 elicited by NoGo stimuli (Table 4).

Table 5. Summary of regression and contrast statistics for the prediction of brain structure changes by age (for corrected alpha, $p = 0.005$).

| Regional Grey Matter | Age $F$-Value | Age $p$ Value | $R^2$ due to Age | Direction & Relative Size of Effect |
|---|---|---|---|---|
| *Cortical grey matter reduced over age* | | | | |
| Ventral Medial Frontal Cortex | 101.14 (L) | $< 0.0001$ | 28.4% | ↓ |
| | 84.84 (R) | | 23.6% | |
| Dorsal Medial Frontal Cortex | 151.86 (L) | $< 0.0001$ | 35.7% | ↓ |
| | 136.72 (R) | | 33.3% | |
| Ventral Lateral Frontal Cortex | 68.08 (L) | $< 0.0001$ | 19.9% | ↓ |
| | 94.12 (R) | | 24.6% | |
| Dorsal Lateral Frontal Cortex | 111.37 (L) | $< 0.0001$ | 28.9% | ↓ |
| | 118.38 (R) | | 32.2% | |
| Inferior Parietal Cortex | 136.04 (L) | $< 0.0001$ | 31.8% | ↓ |
| | 139.32 (R) | | 27.3% | |
| Superior Parietal Cortex | 127.74 (L) | $< 0.0001$ | 33.2% | ↓ |
| | 102.68 (R) | | 33.7% | |
| *Subcortical grey matter relatively preserved over age* | | | | |
| Hippocampus | 16.96 (L) | $< 0.0001$ | 5.8% | ↓ |
| | 21.47 (R) | | 7.3% | |
| Amygdala | 15.17 (L) | $< 0.0001$ | 5.2% | ↓ |
| | 19.89 (R) | | 6.8% | |

Table 6. Summary of regression and contrast statistics for the prediction of eyes closed EEG activity by age (for corrected alpha, $p = 0.001$).

| Brain Function Measure | Age $F$-Value | Age $p$ Value | $R^2$ due to Age | Direction & Relative Size of Effect |
|---|---|---|---|---|
| *Slow EEG activity reduced over age* | | | | |
| Delta Power | 813.24 (Fz) | $< 0.0001$ | 48.4% | ↓ |
| | 909.92 (Pz) | | 45.5% | |
| Theta Power | 638.32 (Fz) | $< 0.0001$ | 41.2% | ↓ |
| | 545.25 (Pz) | | 35.9% | |
| *Faster EEG activity relatively preserved over age* | | | | |
| Alpha Power | 40.65 (Fz) | $< 0.0001$ | 4% | ↓ |
| | 103.35 (Pz) | | 9.6% | |
| Beta Power | 14.84 (Fz) | $< 0.0001$ | 1.5% | ↓ |
| | 24.66 (Pz) | | 2.5% | |

For the EEG, there were reductions in Alpha and Beta power over age, but these were noticeably less pronounced than those for slow-wave power (Table 6).

Similarly, there were less pronounced age-related reductions in grey matter for the limbic hippocampus and amygdala, compared to the cortical regions (Table 5).

### 3.2. *Main effects of genotype*

*"Emotion" time scale*

For ERPs elicited in the timeframe of emotion, there was only one main effect for genotype; the frontal NoGo N200 was reduced in DRD4 2/4 repeat carriers compared to 7 repeat carriers (Table 8).

*"Thinking" time scale*

There were genotype effects for general cognitive measures in the "thinking" time scale. The MAOA Low-activity genotype group showed reduced performance compared to the High-activity genotype group for the sustained attention domain (Table 7). BDNF $Met^{66}$ carriers showed a distinctive pattern of reduced performance

Table 7. Main and interaction effects for genotypes and genotype by age for "thinking" (general cognition) and "self regulation" (social cognition) measures.

| Domain & measure* | Genotype | Genotype main effect | Genotype by age interaction | Total model[a] |
|---|---|---|---|---|
| *"Thinking"* | | | | |
| Executive Function | COMT | — | VV greater decline over age than MM $t = 2.38$, $p = 0.018$ | $F = 29.52$, $p < 0.0001$ |
| Sustained Attention | MAOA | Low < High $F = 4.92$, $p = 0.009$ | — | — |
| Verbal Memory | BDNF | Met < VV $F = 4.00$, $p = 0.047$ | — | — |
| Working Memory Capacity | BDNF | Met < VV $F = 3.61$, $p = 0.055$ | — | — |
| Verbal Processing | BDNF | — | | |
| Sensori-Motor Response Speed | BDNF | — | | |
| *"Self Regulation"* | | | | |
| Emotional resilience | 5HTT | — | Shorts less improvement over age than LL $t = -2.16$, $p = 0.036$ | $F = 17.41$, $p < 0.0001$ |
| Negativity Bias | DRD4 | 2/4R < 7R $F = 4.88$, $p = 0.040$ | — | — |
| Social Skills | DRD4 | 2/4R > 7R $F = 3.65$, $p = 0.028$ | — | — |
| Social Skills | MAOA | Low < High $F = 6.61$, $p = 0.010$ | — | — |

*Where relevant (such as for negativity bias) measures are inverted such that higher scores indicate better performance, and lower scores worse performance, in each case.
[a]Predictors in the total model were genotype, age and genotype-age interaction, in order to determine the contribution of the age-genotype interaction over and above the main effects of age and genotype. There were no significant further interactions with the covariate of sex.

on memory domains (verbal memory and working memory capacity) relative to VV subjects (Table 7).

### *"Self Regulation" time scale*

For social cognition at the "self regulation" time scale, the DRD4 2/4-repeat carriers showed a worse negativity bias, despite better social skills compared to DRD4 7 repeat carriers, consistent with the findings for negativity bias. The negativity bias finding accords with the reduction in early ERPs. For MAOA, the Low-activity genotype also showed reduced social skills compared to the High-activity group (Table 7).

Regional grey matter showed genotype main effects for both COMT and MAOA (Table 9). For COMT, the MM subjects showed significantly reduced grey matter relative to the VV subjects in bilateral ventral medial prefrontal and left ventral lateral prefrontal regions (Table 9). In the High-activity MAOA group, there was significantly reduced grey matter relative to the Low-activity group in bilateral ventral medial prefrontal, left dorsal medial and lateral prefrontal and left inferior and superior parietal cortices (Table 9).

There were no genotype main effects for resting EEG measures of brain activity.

Table 8. Main and interaction effects for genotype and genotype by age for Early ("Emotion" time scale) and Late ("Thinking" time scale) ERPs.

| | Genotype | Genotype Main Effect | Genotype by Age Interaction | Total Model[a] |
|---|---|---|---|---|
| *Late ERPs ("Thinking")* | | | | |
| Selective Attention P300 (Pz) | BDNF | Met < Val | (Met < Val in younger age in particular $t = 2.12$, $p = 0.039$) | |
| *Early ERPs ("Emotion")* | | | | |
| Fear VPP (Fz) | 5HTT | — | Shorts > LL in young but Shorts < LL in older $t = -2.17$, $p = 0.013$ | $F = 63.35$, $p < 0.0001$ |
| Fear VPP (Fz) | MAOA | | Low, less improvement over age than High $t = 2.61$, $p = 0.009$ | $F = 36.30$, $p < 0.0001$ |
| Fear VPP (Fz) | BDNF | — | Met less improvement over age than VV $t = 2.65$, $p = 0.008$ | $F = 4.68$, $p = 0.003$ |
| Automatic "NoGo" N200 (Fz) | DRD4 | 2/4R < 7R $F = 7.67$, $p = 0.006$ | — | — |

[a]Predictors in the total model were genotype, age and genotype-age interaction, in order to determine the contribution of the age-genotype interaction over and above the main effects of age and genotype. There were no significant further interactions with the covariate of sex.

### 3.3. *Genotype by age interactions*

Comparative to the main effects for genotype, there were only isolated interactions between genotype and age for the cognitive and brain measures of interest (Fig. 2). These interactions generally showed that the "risk" allele for each polymorphism contributed to lessening positive effects with age, and to exacerbating negative effects.

*"Emotion" time scale*

The 5HTT-LPR and MAOA polymorphisms showed genotype by age interactions for face ERPs within the time scale of emotion processing. For 5HTT-LPR, Short allele carriers were associated with a greater frontal VPP for fearful face stimuli than the LL group in young individuals, but a smaller VPP in older individuals (Table 8; Fig. 2). The MAOA Low-activity group showed less improvement over age in the frontal VPP for face stimuli than the High-activity group (Table 8; Fig. 2). In a complementary genotype by age interaction, BDNF Met[66] carriers showed less improvement in the frontal VPP for fearful face stimuli, relative to the VV homozygotes (Table 8; Fig. 2).

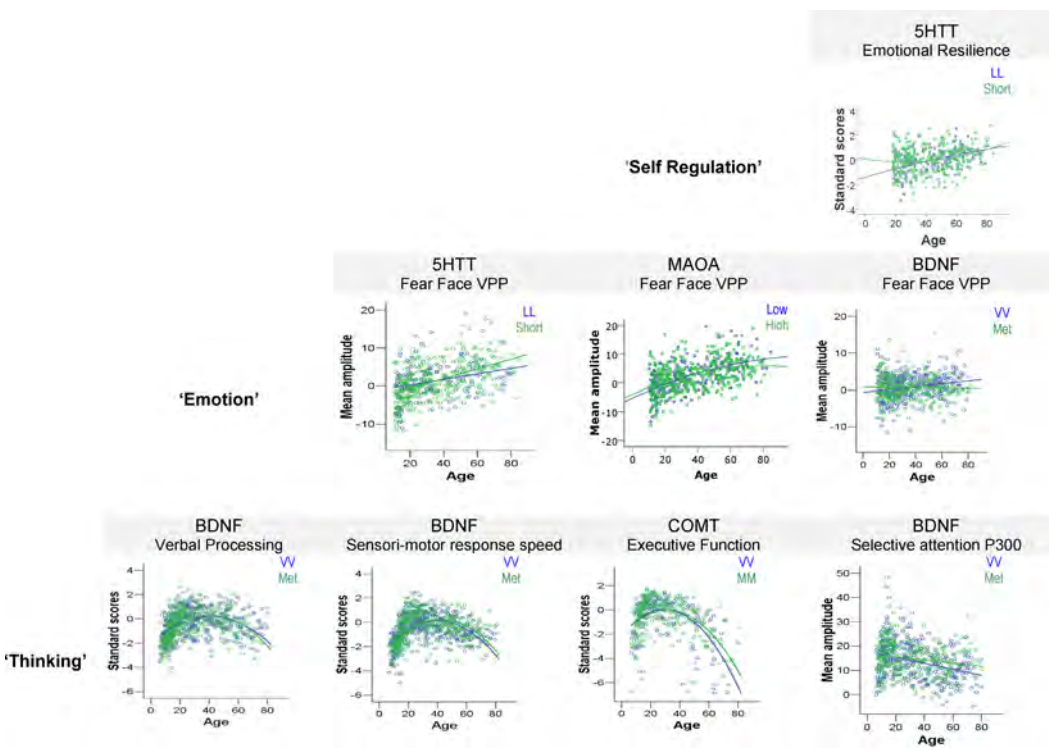


Fig. 2. Summary of genotype by age interactions for "emotion" ERPs and measures of "thinking" (general cognition) and "self regulation" (social cognition).

Table 9. Main and interaction effects for genotypes and genotype by age for brain structure.

| Brain Structure | Genotype | Genotype Main Effect | Genotype by Age Interaction |
|---|---|---|---|
| L Ventral MPFC | COMT | VV < MM $F = 7.13$, $p = 0.010$ | — |
| R Ventral MPFC | COMT | VV < MM $F = 8.32$, $p = 0.006$ | — |
| L Ventral LPFC | COMT | VV < MM $F = 8.17$, $p = 0.006$ | — |
| L Ventral MPFC | MAOA | Low > High $F = 4.67$, $p = 0.037$ | — |
| R Ventral MPFC | MAOA | Low > High $F = 4.98$, $p = 0.028$ | — |
| L Dorsal MPFC | MAOA | Low > High $F = 4.87$, $p = 0.029$ | — |
| L Dorsal LPFC | MAOA | Low > High $F = 4.42$, $p = 0.039$ | — |
| L Superior Parietal | MAOA | Low > High $F = 4.12$, $p = 0.046$ | — |
| L Inferior Parietal | MAOA | Low > High 4.23, $p = 0.041$ | — |

*"Thinking" time scale*

For measures of general cognition, the genotype by age interaction for COMTVal$^{108/158}$Met was due to greater decline in executive function over age for the VV than for the MM genotype (Table 7; Fig. 1).

For ERPs on the "thinking" time scale (200–500 ms), there was a genotype by age interaction for the BDNF Val$^{66}$Met polymorphism in relation to the selective attention parietal P300; in this case Met$^{66}$ carriers showed less decline in the P300 over age than VV homozygotes (Table 8; Fig. 2).

*"Self Regulation" time scale*

For social cognition measures, a genotype by age interaction for the 5HTT-LPR polymorphism and emotional resilience was due to less improvement in emotional resilience for Short allele carriers compared to the LL group (Table 7; Fig. 2).

There were no significant genotype by age interactions for the MRI measures of grey matter. These null results indicate that genetic variants associated with monoamine modulation and plasticity do not contribute to age-related effects of development, maturation and atrophy of brain structure.

There were also no significant genotype by age interactions for the EEG, consistent with the parallelism between brain structure and EEG over age [74].

## 4. Discussion

In this study, we first examined the contribution of age to brain and cognition measures located on the temporal continuum of "emotion", "thinking" and "self regulation" in our INTEGRATE model of brain organization. Second, we examined the possible contribution of genetic polymorphisms involved in monoamine modulation and plasticity to this temporal continuum of processing. Age and genetic variants may be considered key aspects of our disposition (constitutional and genetic), that determine individual differences in the temporal continuum of brain organization.

### *Paradox of aging: Opposing effects for emotion and self regulation versus thinking*

Age (from 6 to 84 years) was found to have opposing effects on brain-behavior measures, depending on the time scale of processing. These opposing effects for "emotion" and "self regulation" versus "thinking" indicated a paradox of aging in which relatively automatic emotional and social functions over both early and longer time scales improve with older age, while more controlled general cognitive functions linked to the thinking time scale show a decline with age. These findings are in contrast to the conventional view that age brings a general neurocognitive decline. They suggest that a broader view of cognition, that encompasses social and emotional domains, is important to revealing areas in which aging brings a specific functional advantage.

Brain function (ERP) measures indicated a preservation or even improvement with age for functions linked to the automatic time scale of emotion processing (within 0–200 ms). While younger individuals showed the lowest level of activation to face stimuli, including fearful expressions, this level increased with age such that the highest level was apparent in older adults. Both the VPP and N200 components, typically elicited automatically within the first 200 ms of stimulus onset were increased with age. The VPP has been linked to automatic orienting to signals of fear, relevant to the minimize danger-maximize reward principle [87]. Correspondingly, the N200 elicited by "NoGo" stimuli increased with age, consistent with evidence for its automaticity [57].

These findings were most apparent for the frontal brain regions, which have similarly been implicated in automatic orienting to significant signals, for both oddball and facial emotion perception tasks [43, 80]. Feasibly, the detection of conflict for "Go" reactions versus their "NoGo" suppression is a crucial aspect of minimizing danger-maximizing reward that occurs automatically with changing task demands, supported by a feedforward mode of brain activity. More controlled response inhibition, associated with the awareness and contextualization of task stimuli, may occur at the somewhat longer time scale of "thinking", and rely on feedback from frontal regions.

Social cognitive functions linked to the longer time scale of "self regulation" (seconds and longer) showed a similar preservation or improvement with age. Older

age was associated with an increasing capacity for positivity (rather than negativity bias) and for emotional resilience. These findings accord with recent evidence that older age brings an improvement in emotional stability and memory for positive versus negative information, together with a shift in medial prefrontal brain activation to signals of danger versus reward [6, 78].

Consistent with a "paradox of aging", brain and behavioral measures associated with the time scale of "thinking" did show the conventional decline with older age, in contrast to findings for the "emotion" and "self regulation" time scales outlined above. The reduction over age for each domain of general cognition was substantial (17 to 30%).[c] Contrasts showed that this decline was particularly evident from 50 years onward. A corresponding decline was apparent for ERPs linked to the "thinking" time scale; the P300 for selective attention to oddball targets, the P300 for sustained attention and the P450 for working memory updating. The P300 is a prominent ERP elicited by selective responses to significant stimuli. Concomitantly, the P450 is elicited by working memory updating, a key aspect of selective attention that allows significant stimuli to be transferred to short and then long-term memory [2]. The decline in P300 and P450 components with age was also most apparent over frontal brain regions, reflecting a "paradox" in regard to the age-related increase in earlier ERPs over the same regions.

Notably, the N200 and P300 (which show opposing effects of age in this study) have also shown opposing effects over time; namely a relative preservation of N200 versus a decline in the P300 [44], consistent with the view that they are capturing relatively automatic versus controlled stimulus processing, respectively. While automatic functions may persist with repeated presentations of a significant stimulus (and be preserved over age), controlled functions may show adaptation to these stimuli.

Measures of brain structure (grey matter from MRI) and resting brain function (EEG) provided convergent evidence for the contribution of age to behavioral and task-related ERP measures. There was a linear loss of cortical grey matter over age, most pronounced for frontal and parietal association cortices. By contrast, grey matter in the limbic hippocampus and amygdala was comparatively preserved, consistent with previous findings [28]. Loss of cortical grey matter over age may be less disruptive to functions supported by a feedforward vs. feedback mode of brain connectivity. Relatively automatic functions at the early "emotion" time scale may be able to proceed in a feedforward mode with sensory input via subcortical networks. In this regard, they remain largely unaffected by the loss of cortical grey matter over age. At the longer time scale of "self regulation", social cognitive functions

[c]We note that the effect of age on these measures of general cognition also fitted a significant quadratic model, indicating that there are distinctive effects on cognition at both younger and older age bands. Curve fitting showed the best fit was a loess function in which the greatest decline in cognition occurs in the older years. Since these effects explained a similar amount of variance (17 to 30%) to linear models, we focused on the linear models in this paper to facilitate comparison of effects with other measures, in which the linear model was the best fit. Yet, future research is warranted to explore the finer-grained variation in cognitive functions in adolescents and children.

may become highly routinized due to the accumulation of experience over the lifespan coupled with their importance to implementing more abstract formulations of minimizing danger and maximizing reward.

On the other hand, "thinking" functions of general cognition that rely on feedback from higher cortical areas may be most disrupted by age-related atrophy in these regions. Of course, this distinction does not account for apparent improvements (and not only preservation) in automatic functions such as emotion perception and negativity bias over age. A possible explanation is that, with the retreat of cortical grey matter, there is a greater reliance on automatic and routinized strategies which become highly efficient. Again, the contribution of life experience, and repeated exposure to negative and positive outcomes, may further refine these strategies. Indeed, social researchers have proposed that there is a shift in the emphasis of core motivational priorities with older age that impacts information processing. This shift represents a greater focus on achieving meaning and satisfaction (abstract forms of reward), as awareness of the finite nature of one's lifespan increases [6].

Resting EEG power followed a similar trajectory over age to grey matter, consistent with previous evidence [74]. In EEG recordings, slow wave Theta and Delta activity showed a particularly marked linear decline with age, with age explaining over 40% of the variance in this slow wave activity. The loss of EEG Alpha and Beta over age, by contrast, was comparatively minimal even though it reached statistical significance. These profiles for Theta/Delta and for Alpha/Beta parallel the pronounced decline in cortical but not subcortical limbic grey matter, respectively. We propose that faster wave EEG (with Alpha cycling at every approximately 100 ms, and Beta even more quickly) corresponds to the automatic time scale of processing, linked to preserved or improved functions in older age. On the other hand, Theta and Delta cycle at the time scale of "thinking" (every approximately 200–300 ms and 500–1000 ms respectively). This distinction accords with evidence that changes in alpha and beta power over time are associated with early ERPs like the N200 rather than the P300, for significant oddball stimuli [44].

### *Genetic disposition and age: Distinctive effects on emotion, thinking and self regulation*

While age showed robust and consistent effects on the brain-behavior measures of interest, genetic variants were found to have more specific effects on these measures.

At the early time scale of "emotion" processing, there was only one isolated effect of these genetic variants. DRD4 2/4 repeat carriers showed a reduced N200 ERP for NoGo stimuli in the Go-NoGo task, relative to 7 repeat carriers. However, there were further effects for the interaction of genotype and age, indicating the way brain-behavior is impacted by genetic disposition may be moderated by the maturational and experiential changes that come with age. The frontal VPP for fearful face stimuli was greater for 5HTT-LPR Short allele carriers than Long allele

homozygotes in younger ages, but the reverse is found in older age. This finding indicates that the normal increase in this ERP with age was not apparent in the Short allele group (despite an initial excess in youth), consistent with its putative role in risk for emotional disorder. Similarly, both the MAOA Low activity group (relatively to High activity) and BDNF Met carriers (relative to VV) showed less of the normal improvement in the fearful face VPP over age. These findings also accord with indications that the MAOA Low activity variant and BDNF Met allele contribute to risk for emotion-related disturbances [21, 22, 83], which may have peak ages of onset.

For the longer time scale of "self regulation", DRD4 2/4 repeat carriers were associated with a relatively worse negativity bias (compared to 7 repeat carriers) — corresponding to the reduction in the NoGo ERP at the earlier "emotion" time scale. The MAOA Low activity group showed a similar reduction in social skills compared to the high activity variant. For the genotype interactions with age, results for the 5HTT-LPR also complemented those for the "emotion" time scale. The Short allele carriers showed less improvement in emotional resilience over age than the LL homozygotes.

For the "thinking" time scale, relative reductions in general cognitive functions were apparent for MAOA Low activity and BDNF Met groups; for sustained attention for the MAOA Low activity group, and for both verbal memory and working memory capacity for BDNF Met carriers. BDNF Met carriers showed a corresponding reduction relative to the Val group on the parietal P300 elicited by oddball targets. There was only one interaction with age, in which the COMT VV group (associated with risk for prefrontal-mediated cognitive disturbances) showed a greater decline in executive function over age than the MM group.

Notably, there were no genotype by age interactions for grey matter or for resting EEG power. These null findings are important in indicating that the moderation of these genetic effects on information processing by age are constrained to very specific effects on task or stimulus-related processing. Feasibly, these effects indicate that life experience associated with age contributes more to the genotype-age interactions than do biological factors in development and maturation — especially in light of the null effects for grey matter. Main effects of genotype were apparent for grey matter but not EEG; the COMT VV (relative to MM) showed less grey matter for ventral medial and lateral prefrontal regions, while the MAOA Low activity (relative to High activity) variant was associated with higher grey matter compared for the prefrontal cortex (spanning dorsal, ventral and medial and lateral sectors) and left superior and inferior parietal cortices.

## 5. Conclusion

We propose the INTEGRATE Model, which draws on an integrative neuroscience framework, and highlights the organizing principle of "minimize danger-maximize

reward". In this study, the INTEGRATE Model was applied to examining the contributions of age and genetic disposition to Emotion, Thinking and Self Regulation. The results suggested a "paradox of aging", in which Thinking functions of memory, attention and information processing efficiency declined with older age, while functions of Emotion and Self Regulation, including negativity bias and emotional resilience, improved with age. Age had relatively minimal effects on moderating the effect of genetic variants on these functions. The paradox of aging has implications for the overwhelming increase in age-related illnesses predicted by the "demographic revolution" in the world's population. New approaches drawing on these findings and application of the INTEGRATE Model, may be used to develop more personalized and effective strategies for addressing age-related difficulties. It would also be important to expand this research into disorders of mental health, given that both age and genetic variants modulating the disruptions to Emotion, Thinking and Self Regulation are implicated in susceptibility to these disorders.

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LMW and CRC are minor shareholders (<1%) in Brain Resource (BR). LMW, JMG and DMP have received fees from BR for work unrelated to this study. EG is CEO of BR, with significant financial interest in company. However, we note that scientific decisions about research and publication using the Brain Resource International Database are made by a scientific network (Brain Research and Integrative Neuroscience Network, BRAINnet; see www.brainnet.net), which is independently administered via a peer-review process. BR had no direct involvement in the design and implementation of the project.

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