Unravelling the Language of the Mind: Exploring the Intersection of Language, Consciousness, and Wellbeing through the Lens of Psychedelics

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I, Regan Harle, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Regan Harle, 27th September 2024

Abstract

This thesis explores the neural correlates of language processing and its relationship to wellbeing, followed by an investigation into how N,N-Dimethyltryptamine (DMT) alters brain activity related to language processing. The initial focus is on understanding how different wellbeing-related word categories (e.g., cognitive, emotional, social) are processed across the brain. Using neuroimaging data from the Naturalistic Neuroimaging Database (NNDb), the research provides support for the idea that language processing is not confined to static "language centres" but involves a distributed network of regions, including those responsible for emotional regulation, social cognition, and self-referential thought. A Support Vector Machine (SVM) model was used to predict wellbeing based on neural responses to these language stimuli. Furthermore, through meta-analyses of all neuroimaging psychedelic and ketamine studies, the second chapter provides a comprehensive overview of how language processing mediates psychedelic-induced changes in conscious experience. The analysis shows that psychedelics induce alterations in conscious experience by disrupting neural networks responsible for language processing, suggesting that these networks play a key role in shaping subjective consciousness. Furthermore, the UNITy study investigates brain activity as participants watch a movie in an fMRI scanner, similar to the NNDb. These effects were further validated using the previously developed SVM model which predicted wellbeing outcomes based on changes in neural activity patterns when processing the chosen word categories. The results align with Jeremy Skipper's HOLISTIC theory, which posits that language is not merely a localised cognitive function but a multi-modal process that draws on sensory, motor, and emotional networks. The research demonstrates that both language processing and psychedelic experiences involve distributed neural systems, offering new perspectives on how language shapes consciousness and how psychedelics modulate these processes to promote neuroplasticity and psychological wellbeing. This work contributes to the broader understanding of how language, consciousness, and psychedelics interact, with important implications for the future development of psychedelic-assisted aid for mental health disorders.

Impact Statement

The research presented in this thesis offers significant contributions to the fields of neurobiology, psychopharmacology, and mental health. By integrating advanced neuroimaging techniques, machine learning models, and comprehensive theoretical frameworks, this work elucidates the complex interactions between language, consciousness, and psychedelics. The following are the key impacts of this research:

- **Comprehensive Understanding of Psychedelic Effects:** This thesis provides a detailed meta-analysis of existing neuroimaging studies on classic psychedelics and ketamine, revealing how these substances modulate neural circuits involved in language processing and self-referential thought. By investigating the role of language-related brain processes in mediating the subjective effects of psychedelics on consciousness, this research unveils a crucial mechanism underlying the profound alterations in perception, cognition, and self-awareness induced by these compounds. This provides compelling evidence for the involvement of language networks in shaping the phenomenology of psychedelic experiences, opening new avenues for understanding the neurobiology of altered states of consciousness.
- **Integration of Language and Consciousness:** By exploring the role of language in shaping conscious experience, this research highlights the interconnectedness of linguistic processing and self-awareness. The application of predictive modelling techniques to fMRI data demonstrates that language-based neural activity can serve as a marker for wellbeing, underscoring the importance of linguistic analysis in cognitive neuroscience. Additionally, this thesis contributes to a broader shift in our conceptualisation of mental health and wellbeing. It emphasises the importance of considering the complex interplay between language, subjective experience, and neural processes in promoting psychological flourishing and resilience.
- **Neuroplasticity and Mental Health:** The investigation into the neuroplastic effects of psychedelics, particularly through the UNITy study, provides empirical evidence that psychedelics promote structural and functional neural plasticity. These findings have significant implications for the development of novel therapeutic approaches for mental health conditions, such as depression, anxiety, PTSD, and addiction. By demonstrating that psychedelic-induced neuroplasticity enhances cognitive and emotional flexibility, this research supports the potential of psychedelics as tools for mental health treatment.

- **Psychedelic-Assisted Psychotherapy:** With the insights from predictive modelling, a comprehensive framework is offered for understanding how these therapies can be optimised. The research highlights the importance of integrating linguistic and neuroimaging data to tailor therapeutic interventions, ultimately improving patient outcomes.
- **Support for HOLISTIC Theory:** Importantly, this thesis synthesises findings across multiple domains, including psychedelics, neuroscience, linguistics, and wellbeing research, under the unifying framework of the HOLISTIC theory (Higher Order Language and Inner Speech To "I" Consciousness). Support for this theory in the context of psychedelic experiences offers new avenues for research and theoretical development in cognitive neuroscience, furthering understanding of the mind-brain relationship, and bridging the gap between subjective experience and neural dynamics.
- **Predictive Modelling in Neuroscience:** The development of a language-based predictive model of wellbeing using fMRI data represents a significant methodological advancement. This innovative approach showcases the power of leveraging language-related neural patterns to predict and understand subjective states of wellbeing, paving the way for the creation of novel diagnostic and therapeutic tools that harness the intimate connection between language and mental health. The application of this predictive model to investigate the impact of DMT-induced neuroplasticity on wellbeing also offers insights into the therapeutic potential of psychedelics. By elucidating the mechanisms through which these compounds reshape language-related brain networks and influence subjective experiences, this research lays the foundation for the development of targeted psychedelic-assisted interventions that optimise mental health outcomes.
- **Improved Mental Health Interventions:** The impact of this research extends beyond academia, holding implications for mental health care and society at large**.** The insights gained from this research have the potential to inform clinical practices and policy-making related to mental health treatment. By providing evidence for the therapeutic benefits of psychedelics and the importance of language in mental health, this work advocates for a more integrated, personalised and holistic approach to mental health care.
- **Public Understanding and Acceptance:** This thesis contributes to the growing body of evidence supporting the safe and effective use of psychedelics in therapeutic settings. By disseminating these findings, the research helps to reduce stigma and promote public

understanding of the benefits and mechanisms of psychedelic approaches to health and wellbeing.

In conclusion, this thesis represents a significant advancement in our understanding of the language of the mind and its implications for consciousness, psychedelics, and well-being. By integrating cutting-edge neuroscientific methods, innovative theoretical frameworks, and a cross-disciplinary approach, this research paves the way for a new era of psychedelic science and mental health care, ultimately contributing to the betterment of the human condition.

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Abbreviations

Word	**Abbreviation**
5-methoxy-N,N-dimethyltryptamine	5-MeO-DMT
Activation Likelihood Estimation	ALE
Alcohol use disorder	AUD
Altered states of consciousness	ASCs
Angular gyrus	AG
Anterior cingulate cortex	ACC
Basal ganglia	BG
Brain-derived neurotrophic factor	BDNF
Cognitive Behavioural Therapy	CBT
Convolutional Neural Network	CNN
Cortico-striato-thalamo-cortical	CSTC
Default Mode Network	DMN
Developmental language disorder	DLD
Diffusion tensor imaging	DTI
Dorsolateral prefrontal cortex	DLPFC
Dynamic Causal Modelling	DCM
Electroencephalography	EEG
Entropic brain theory	EBT

False discovery rate	FDR
False negative	FN
False positive	FP
False positive rate	FPR
Family-wise error	FWE
Frontoparietal network	FPN
Functional connectivity	FC
Functional magnetic resonanceimaging	fMRI
General Linear Model	GLM
Global Workspace Theory	GWT
Hallucinating persisting perceptual disorders	HPPD
Hemodynamic response function	HRF
Higher Order Language and Inner Speech to "I" Consciousness	HOLISTIC
Higher Order Theories	HOT
Independent component analysis	ICA
Inferior frontal gyrus	IFG
Integrated Information Theory	IIT
Intersubject correlation	ISC
Lateral prefrontal cortex	LPFC

Leave-one-out cross-validation	LOO-CV
Left hemisphere	LH
Linear mixed effects model	LME
Linguistic Inquiry and Word Count	LIWC
Logistic Regression	LR
Long term potentiation	LTP
Lysergic acid diethylamide	LSD
Machine learning	ML
Magnetoencephalography	MEG
Maximum-Likelihood Estimation	MLE
Medial prefrontal cortex	mPFC
Middle tempotal gyrus	MTG
Montreal Neurological Institute	MNI
Multilevel Kernel Density Analysis	MKDA
Multivariate Pattern Analysis	MVPA
N,N-dimethyltryptamine	DMT
Naturalistic Neuroimaging Database	NNDb
Near death experience	NDE
Neural correlates of consciousness	NCC
Neural network	NN
Parkinson' Disease	PD

Positron emission tomography	PET
Post-traumatic stress disorder	PTSD
Posterior parietal cortex	PCC
Posterior superior temporal gyrus	pSTG
Posterior superior temporal sulcus	pSTS
Preferred Reporting Items for Systematic Reviews and Meta-Analyses	PRISMA
Prefrontal cortex	PFC
Psychedelic assisted psychotherapy	PAP
Random Forest	RF
Rapid eye movement	REM
Rectified linear unit	ReLU
Relaxed beliefs under psychedelics	REBUS
Right hemisphere	RH
Salience network	SN
Seed-based d Mapping with Permutation of Subject Images	SDM-PSI
Serotonin	5-HT
Serotonin 2A receptor	5-HT2A
Signal-to-noise ratio	SNR
Specific language impairment	SLI

Superior temporal gyrus	STG
Supplementary motor area	SMA
Support Vector Machine	SVM
Talairach	TAL
Temporoparietal junction	TPJ
Theory of Mind	TOM
Threshold-Free Cluster Enhancement	TFCE
Traumatic brain injury	TBI
True negative	TN
True positive	TP
Understanding Neuroplasticity Induced by Tryptamines	UNITy
Ventromedial prefrontal cortex	vmPFC
World Health Organisation	WHO

Glossary

Term	**Definition**
5HT2A Receptor	A subtype of serotonin receptor found in the brain and involved in various functions, including mood, perception, and cognition. Activation of this receptor is thought to play a role in the effects of psychedelic drugs.
Activation Likelihood Estimation (ALE)	A method for meta-analysis in neuroimaging.
Amygdala	A brain region associated with processing emotions, particularly fear and aggression.
Anterior Cingulate Cortex (ACC)	A brain region involved in cognitive control, decision-making, and emotional regulation.
Aphasia	A language disorder caused by brain damage that affects a person's ability to communicate.
Arcuate Fasciculus	A white matter tract connecting Broca's area and Wernicke's area in the brain, thought to be involved in language processing.
Auditory Cortex	The part of the brain that processes sounds.
Basal Ganglia	A group of brain structures involved in motor control, learning, and reward processing.
Broca's Area	A region in the frontal lobe of the brain's left hemisphere associated with language production. Damage to this area can result in language production impairments, highlighting its importance in articulation and grammar.
Cerebellum	A brain region traditionally associated with motor control but also plays a significant role in the timing and sequencing of speech production.
Cerebral Cortex	The outermost layer of the brain, responsible for higher cognitive functions.
Cognitive Behavioural Therapy (CBT)	A psychotherapeutic approach that aims to change patterns of thinking or behaviour that are causing people's problems.
Cognitive Flexibility	The ability to switch between different tasks or mental sets.
Cognitive Words	Words that indicate higher-level thinking and psychological adjustment.

Claustrum	A thin sheet of gray matter located deep within the cerebral cortex, potentially involved in consciousness.
Concrete Words	Words that refer to tangible objects or specific experiences, such as 'apple,' 'car,' or 'happiness.'
Consciousness	The state of being aware of and responsive to one's surroundings.
Default Mode Network (DMN)	A network of brain regions, including the medial prefrontal cortex (mPFC) and posterior cingulate cortex (PCC), that is active during introspection and self-referential thought.
Depression	A mental disorder characterised by persistent sadness and loss of interest in activities.
Dorsal Stream	A neural pathway involved in processing the 'how' of actions, including the production of speech.
Dorsolateral Prefrontal Cortex (dlPFC)	A brain region important for working memory and executive functions.
Dual Stream Model	A model of language processing that proposes two distinct pathways for processing sound (dorsal stream) and meaning (ventral stream).
Dyslexia	A learning disorder that affects reading and language processing abilities.
Ego Dissolution	Refers to the experience of losing one's sense of self, often reported during high doses of psychedelics. It is characterised by a temporary disintegration of personal boundaries and identity.
Electroencephalography (EEG)	A technique for measuring brain activity using electrodes placed on the scalp.
Embodied Cognition	The idea that cognition is shaped by our bodily experiences and interactions with the world.
Entropic Brain Hypothesis	The theory that psychedelics increase the entropy of brain activity, leading to a more flexible and less predictable state.
Executive Functions	Higher-level cognitive processes such as planning, decision-making, and working memory.
False Positive (FP)	An incorrect classification in which a non-existent effect is detected.
False Negative (FN)	A missed detection of an actual effect.
First-Person Pronouns	Llinked to self-referential processing and can indicate a focus on the self, e.g., 'I,' 'me.'

Functional Connectivity (FC)	Refers to the temporal correlation between spatially remote brain regions.
Functional Magnetic Resonance Imaging (fMRI)	A neuroimaging technique that measures brain activity by detecting changes in blood flow.
Fusiform Gyrus	A brain region involved in facial recognition and visual processing.
General Linear Model (GLM)	A statistical model used to analyse fMRI data.
Global Workspace Theory	A theory of consciousness that suggests that conscious experience arises from the integration of information across a distributed network of brain regions.
Hallucinations	Perceptions of sights or sounds that are not actually present.
Higher Order Thought (HOT)	The theory posits that consciousness arises when a mental state is the object of a higher-order representation. This means that for an individual to be aware of a thought, there must be a second-order thought that reflects on the first-order mental state.
Hippocampus	A brain region crucial for memory formation and spatial navigation.
HOLISTIC Theory	The Higher Order Language and Inner Speech To "I" Consciousness model, which posits that language is not merely a localised cognitive function but a multi-modal process that draws on sensory, motor, and emotional networks.
Hypnosis	A state of consciousness characterised by focused attention and increased suggestibility.
Independent Component Analysis (ICA)	A statistical method for separating mixed signals.
Inferior Frontal Gyrus (IFG)	A brain region in the frontal lobe involved in language processing and cognitive control.
Integrated Information Theory (IIT)	A theory of consciousness that suggests that consciousness is related to the amount of integrated information a system has.
Inner Speech	The experience of internally verbalising thoughts.
Insula	A brain region involved in interoception, emotion, and self-awareness.
Interospection	The sense of the internal state of the body, including sensations related to hunger, thirst, and emotional states.
Introspection	The examination or observation of one's own mental and emotional processes.

Language	A multi-level system encompassing not only the traditional aspects of communication, such as phonology, syntax, and semantics, but also higher-order cognitive functions like inner speech
Language Network	Should be understood as including not only traditional language areas like Broca's area (inferior frontal gyrus, IFG) and Wernicke's area (posterior superior temporal gyrus, pSTG), but also other key regions. Traditional language-related regions are integral nodes within a larger, interconnected network. While these areas play critical specialised roles in linguistic functions—syntax, lexical-semantic access, and phonological processing—their functionality is heavily dependent on extensive communication with other cognitive, emotional, and motor regions. These include the anterior superior temporal gyrus (aSTG), crucial for semantic processing; the inferior parietal lobule (IPL), involved in integrating phonological and semantic information; and prefrontal regions like the dorsolateral prefrontal cortex (dlPFC), contributing to higher-order cognitive control and integration of language with other cognitive functions. Furthermore, the medial prefrontal cortex (mPFC) and precuneus, should also be considered part of this extended language network. This network, therefore, extends beyond the traditionally defined language areas and includes regions crucial for the integration of linguistic information with other cognitive processes, including those related to self-awareness and consciousness. This integrated perspective aligns with the HOLISTIC theory proposed by Skipper, which emphasises the multi-modal and distributed nature of linguistic cognition, bridging traditionally isolated ‘language regions’ with the broader neural systems implicated in consciousness and wellbeing. In this thesis, this mostly comprises the map in Figure 1.
Lateralisation	The specialisation of functions in one hemisphere of the brain.
Lexical-Semantic Access	Refers to the process of retrieving the meaning of words from memory. It is crucial for language comprehension and production, and regions like Wernicke's area are implicated in this process.
Lifestyle Terms	Refers to words that describe behaviours and choices related to health and wellbeing, such as 'exercise,' 'diet,' and 'socialising.'
Linear Mixed Effects Model (LME)	A statistical model accounting for both fixed and random effects.
Linguistic	Relating to language.

Linguistic Patterns	Refers to the specific ways in which language is used, including word choice and structure
LSD	A potent psychedelic drug that alters perception and thought.
Machine Learning (ML)	A subset of AI that enables computers to learn patterns from data.
Magnetic Resonance Imaging (MRI)	A neuroimaging technique that provides detailed images of brain structure.
Medial Prefrontal Cortex (mPFC)	Involved in self-referential thought and emotional regulation.
Meditation	A practice of focused attention and mindfulness to achieve a mentally clear and emotionally calm state.
Mental Health	A person's emotional, psychological, and social wellbeing.
Meta-Analysis	A statistical technique used to combine the results of multiple studies.
Mystic Experiences	Characterised by feelings of unity, interconnectedness, and transcendence of the self. These experiences are commonly reported during psychedelic use.
Narrative Self	The idea that our sense of self is constructed through the stories we tell ourselves about our lives.
Naturalistic Stimuli	Stimuli that are similar to those encountered in real-life situations.
Negation Words	Words expressing denial or contradiction (e.g., 'no,' 'never').
Negative Words	Words that carry a negative emotional charge.
Neural Correlates of Consciousness (NCC)	The specific brain activity patterns linked to conscious experience.
Neural Integration	Refers to the process by which different brain regions communicate and coordinate their activities.
Neurobiology	The study of the nervous system.
Neuroimaging	Techniques for visualising brain structure and function.
Neurone	A nerve cell in the brain that transmits information.
Neuroplasticity	The brain's ability to reorganise itself by forming new neural connections throughout life.
Neurotransmitter	A chemical messenger that transmits signals between neurones.
N,N-Dimethyltryptamine (DMT)	A powerful psychedelic compound found in certain plants.

Occipital Lobe	The part of the brain that processes visual information.
Parietal Lobe	The part of the brain that processes sensory information, including touch, temperature, pain, and pressure.
Perception	The process of organising and interpreting sensory information to give meaning to objects and events.
Perception Words	Words related to sensory experience (e.g., 'look,' 'feel,' 'hear').
Phonology	The study of the sound system of language.
Placebo	A substance with no known medical effects, used as a control in clinical trials.
Positive Words	Words that evoke positive emotions or associations.
Positron Emission Tomography (PET)	A neuroimaging technique for measuring brain metabolism.
Predictive Coding	A theory of brain function that suggests that the brain constantly generates predictions about the world and updates these predictions based on sensory input.
Prefrontal Cortex (PFC)	A brain region crucial for executive functions such as decision-making, planning, and self-reflection. It plays a significant role in maintaining and manipulating information in working memory, which is essential for sustained conscious awareness.
Psychedelics	Substances that induce profound shifts in perception, emotion, cognition, and consciousness. These compounds, such as psilocybin and LSD, are known to promote neuroplasticity.
Psychedelic-Assisted Psychotherapy (PAP)	A form of therapy that combines the use of psychedelic drugs with psychotherapy to treat mental health conditions.
Psychosis	A mental health condition characterised by a disconnection from reality, often involving hallucinations and delusions
Random Forest	A machine learning algorithm used for classification and regression tasks.
REBUS (Relaxed Beliefs Under Psychedelics)	A whole-brain model that suggests that psychedelics work by relaxing the brain's prior beliefs about the world, allowing for new experiences and insights.
Receptor	A protein on the surface of a cell that binds to specific molecules, such as neurotransmitters.

Rectified linear unit (ReLU)	A type of activation function used in artificial neural networks.
Salience Network (SN)	A neural network that detects and filters important stimuli.
Second-Person Pronouns	Relate to direct address and social interaction, e.g. 'you.'
Self-Referential Words	Words including first-person, second-person and third-person pronouns.
Semantic Processing	The aspect of language processing that deals with meaning.
Social Cognition	Refers to the processes by which people understand and interpret social information
Social Words	Words, such as 'friend' and 'family.'
Specific Language Impairment (SLI)	A language disorder that affects a person's ability to acquire and use language.
Speech	The expression of thoughts and feelings by articulate sounds.
Striatum	A subcortical structure in the brain associated with motor control and reward.
Superior Temporal Gyrus (STG)	A brain region in the temporal lobe involved in auditory processing and language comprehension.
Synaptogenesis	The formation of new synapses between neurones.
Syntax	The arrangement of words and phrases to create well-formed sentences in a language.
Thalamocortial System	This system involves the thalamus and the cortex and is crucial for conscious information processing. Disruptions to thalamocortical loops, such as during anaesthesia or deep sleep, can lead to a loss of consciousness
Tempoparietal Junction (TPJ)	A brain region involved in social cognition and theory of mind.
Temporal Terms	Words that relate to time, including past ('was'), present ('is'), and future ('will').
Third-Person Pronouns	Relate to social interaction and perspective-taking, e.g., 'he,' 'she,' 'they.'
True Positive (TP)	A correct classification in statistical analysis.
True Negative (TN)	A correct rejection in classification.
Tryptamines	A class of psychoactive compounds that include substances like DMT and psilocybin.

Ventral Stream	A neural pathway involved in processing the 'what' of actions, including the comprehension of language.
Ventral Striatum	A brain region involved in reward processing and motivation.
Ventromedial Prefrontal Cortex (vmPFC)	A region responsible for emotion regulation and decision-making.
Visual-Lexical Pathway	Involves the processing of visual information related to language, particularly in recognising written words.
Wellbeing	Encompasses a holistic state of health, happiness, and prosperity, reflecting not only the absence of illness but also the presence of positive mental states and life satisfaction. In this thesis, this was quantified by NIH toolbox psychological measures, including General Life Satisfaction, Meaning and Purpose and Positive Affect. General Life Satisfaction is a computer-adaptive test (CAT) or fixed form (FF) assessment of the participant’s cognitive evaluation of life experiences and whether the participant likes his or her life. Meaning and Purpose is a computer-adaptive test (CAT) assessment of feelings around whether life has purpose and there are good reasons for living, including hopefulness, optimism, and goal-directedness. Positive Affect is a computer-adaptive test (CAT) assessment of feelings of pleasurable engagement with the environment, such as happiness, joy, excitement, enthusiasm, and contentment.
Wernicke's Area	A region in the temporal lobe of the brain associated with language comprehension.

Chapter 1: Introduction

Although often viewed as vastly different aspects of our being, language and consciousness complement each other in ways that old philosophers could not have imagined. Language, a physical phenomenon produced by the body, allows us to communicate our experiences. Rene Descartes described it as one of the furthest aspects from consciousness, our subjective awareness and perception of reality. In his Meditations on First Philosophy, Descartes noted, "There is a great difference between mind and body, inasmuch as body is by nature always divisible, and the mind is entirely indivisible" (Descartes, 2000; Kotchoubey, 2018). Similarly, Locke's theory of the "tabula rasa," or blank slate, argued that language was separate from consciousness itself and purely arose as a social and cultural construct. Locke asserted in An Essay Concerning Human Understanding, "Words in their primary or immediate Signification, stand for nothing, but the Ideas in the Mind of him that uses them" (Locke, 1690). Immanuel Kant, a more recent philosopher, held similar beliefs, arguing that language was part of the phenomenal realm (objects of sensory experience) whereas consciousness belonged to the noumenal realm of the mind (things-in-themselves). He articulated in Critique of Pure Reason, "Thoughts without content are empty, intuitions without concepts are blind" (Kant, 1908).

For centuries, under the influence of Descartes, the relationship between language and consciousness was viewed through the lens of Cartesian dualism by many philosophers. At the time, thinkers posited the idea of the mind (consciousness) and body being separate entities, with language, processed in the brain, thus seen as distinct from the non-physical realm of consciousness (Barnett, 2014).

However, modern research has challenged these traditional dichotomies. Neuroscience, psychology, and linguistics have unveiled intricate connections between language and consciousness, revealing that they are not merely distinct entities but deeply intertwined aspects of human cognition. Understanding this link has profound implications for fields ranging from mental health treatment to cognitive enhancement (Kivinen & Piiroinen, 2012). This literature review aims to synthesise current knowledge on the neurobiology underpinning language and consciousness, exploring their intersection and the potential role of psychedelic substances in modulating these processes.

The Neurobiology of Language

Language can be broadly defined as a system of communication that utilises symbols, sounds, or gestures to convey meaning, encompassing both spoken and written forms as well as non-verbal cues (Kewenig et al. 2022; Doedens and Meteyard 2022; Jackendoff, 2002). For the purposes of this thesis, and aligning with Skipper et al. (2022), I more specifically define language as a multi-level system encompassing not only the traditional aspects of communication, such as phonology, syntax, and semantics, but also higher-order cognitive functions like inner speech. This definition moves beyond a purely communicative view of language and encompasses its role in internal thought processes and self-awareness. It is important to note that this definition is not universally accepted, and the boundaries of 'language' are subject to ongoing debate (as noted later).

This section will explore the brain regions involved in language processing, the neural networks that underlie it, the theories of how language is acquired and developed, and the neurobiological basis of language disorders.

Typical brain regions involved in language processing

Broca's area

In 1861, French surgeon Paul Broca made a seminal discovery in the field of language production. After observing brain lesions in the left hemisphere (LH) of patients with language production impairments, he pinpointed a posterior section of the inferior frontal gyrus (IFG) as crucial for articulation (Tremblay & Dick, 2016). This area, now eponymously known as Broca's area, encompasses the pars triangularis (approximately Brodmann area 45) and pars opercularis (approximately Brodmann area 44), and is crucial in syntactic processing (Amunts et al., 1999; Skipper et al., 2017).

Wernicke's area

A decade later, in 1874, German neurologist Carl Wernicke made another pivotal discovery. Through autopsies of two patients with difficulties comprehending language, he identified lesions in the left superior temporal gyrus (STG) (Wernicke, 1969) 1874). This region, known as Wernicke's area, became particularly associated with the posterior STG (pSTG) and is implicated in language comprehension, lexical-semantic access, and sentence interpretation

(Geschwind, 1970). However, the precise delineation of Wernicke's area has been a subject of ongoing debate, with various interpretations encompassing regions beyond the pSTG (Bogen & Bogen, 1976; M.-M. Mesulam et al., 2015).

Initially, Wernicke proposed that the "auditory images" were located throughout the entire STG, based on the assumption that subcortical auditory pathways projected there. By 1881, Wernicke expanded his description when he drew a hatched area covering much of the left STG (Wernicke, 1881). Despite these refinements, subsequent interpretations varied widely, extending the region to include the inferior parietal lobe, middle temporal gyrus (MTG), and even angular gyrus (AG) in some cases (Binder et al., 2009; Bogen & Bogen, 1976).

Geschwind’s classic model

In 1970, American neurologist Norman Geschwind proposed a model linking Broca's and Wernicke's areas via the arcuate fasciculus, a white matter tract thought to integrate language production and comprehension (Catani et al., 2005; Geschwind, 1970). However, this classic model has faced criticism for its oversimplification. First, it is centred on two "language regions" while largely ignoring subcortical structures and relevant connections. Second, its limited spatial extent and cortical focus make it difficult to reconcile the model with modern knowledge about the white matter connectivity supporting speech and language function (Skipper et al., 2017; Tremblay & Dick, 2016).

Contemporary research has expanded our understanding of language neurobiology, emphasising the intricate network of brain regions involved in language processing beyond Broca's and Wernicke's areas. Studies have highlighted the lateralisation of auditory-language pathways, the plasticity of language cortex, and the functional connectivity within language networks (Lebel & Beaulieu, 2009; Parker et al., 2005). Furthermore, investigations into language disorders like aphasia and schizophrenia have shed light on the complex interplay between different brain regions in language function (Tomasi & Volkow, 2012; Xiang et al., 2010). Therefore, modern research underscores the need to consider a broader network of brain regions and connections involved in language comprehension and production. By exploring the complexities of language neurobiology beyond the classic model, we can gain deeper insights into the neural substrates of language and its disorders.

Language disorders and their neurobiological basis

The limitations of the classic model, particularly the lack of a consistent anatomical definition for Wernicke's area, have spurred researchers to investigate language disorders and employ advanced neuroimaging techniques to refine our understanding of the neural substrates of language processing.

Aphasia

The investigation of language disorders, such as aphasia, specific language impairment (SLI), and dyslexia, has further shed light on the neural underpinnings of language. Aphasia, resulting from localised brain damage, manifests in diverse forms depending on the affected region, thus revealing the distinct roles of various cortical areas in language functions (Ardila, 2010). For instance, Broca's aphasia is characterised by non-fluent speech and difficulties in syntactic processing due to damage in Broca's area, whereas Wernicke's aphasia involves fluent but nonsensical speech and poor comprehension, indicating the critical role of Wernicke's area in language understanding.

Specific language impairment, dyslexia & developmental language disorders

Alternatively, SLI and dyslexia are frequently associated with structural and functional anomalies in language networks, underscoring the significance of neural connectivity and plasticity (Krishnan et al., 2016). These disorders often involve abnormalities in regions such as the left temporoparietal junction (TPJ), which is important for phonological processing and word recognition (Kershner, 2019). Moreover, developmental language disorders (DLDs) have been linked to disruptions in the typical trajectory of language network specialisation and maturation (Friederici, 2006). Recent neuroimaging evidence suggests potential associations with atypical brain development or structural abnormalities in language-related regions, highlighting the importance of early detection and intervention.

Neuroimaging findings

Advancements in neuroimaging techniques like functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) have revolutionised our understanding of language processing. These technologies have shown that regions beyond the classical language areas, including parts of the right hemisphere (RH), basal ganglia, and cerebellum, are crucial contributors to various linguistic tasks (Price, 2012). For example, the RH is involved in processing prosody and metaphorical language, while the basal ganglia and cerebellum contribute to motor planning and coordination necessary for speech production. These findings emphasise the importance of considering the entire brain network when studying language processing, rather than focusing solely on isolated cortical regions.

The Dual Stream Model

A prominent framework that captures the distributed nature of language processing is the dual stream model proposed by (Hickok & Poeppel, 2004). This model posits two primary pathways for language processing:

- Dorsal Stream (Sound to Action): This pathway links the auditory cortex to the motor cortex, specifically connecting the posterior temporal lobe to the frontal lobe. It is primarily implicated in phonological processing (the sound of language) and supports language production (speech, sign language, or writing).
- Ventral Stream (Sound to Meaning): This pathway connects the auditory cortex to regions associated with semantics, particularly linking the frontal lobe to the temporal lobe via the MTG and IFG. It is involved in processing word and sentence meaning, vocabulary access, and comprehension of complex sentence structures.

Empirical evidence from DTI studies (Saur et al., 2008) and lesion studies (Buchsbaum et al., 2011; Dronkers et al., 2004; Friederici, 2012; Gorno-Tempini et al., 2004) has largely corroborated the distinct roles of these pathways in phonological and semantic processing, respectively. However, the model has been criticised for its simplicity, with emerging evidence suggesting an even more distributed architecture involving dynamic interactions across multiple cortical areas (Bornkessel-Schlesewsky & Schlesewsky, 2013).

Beyond the dual stream model: a distributed language network

Price (2012) and Skipper (2014) advocate for a more comprehensive view, highlighting the involvement of the cerebellum and basal ganglia, traditionally associated with motor control and coordination. Indeed, speech and language functions engage a vast number of brain regions that extend far beyond "Broca's" and "Wernicke's" areas, in the frontal, parietal, and temporal lobes, in the medial hemispheres of the brain, as well as in the basal ganglia, thalamus, and cerebellum (Crosson, 2013; Hebb & Ojemann, 2013; Mariën et al., 2014; Price, 2010).

The cerebellum

The cerebellum is implicated in the timing and sequencing of speech production and the modulation of linguistic output (Ackermann et al., 2007; Stoodley & Schmahmann, 2009). fMRI studies have shown cerebellar activation during various language tasks, including verb generation, reading, and syntactic processing (Skipper & Lametti, 2021; Stoodley & Schmahmann, 2009). The cerebellum's involvement in language processing may relate to its role in coordinating complex, sequential activities, which are essential for fluent speech and the integration of syntactic structures. Moreover, cerebellar damage has been associated with dysarthria and other speech production deficits, further supporting its contribution to the language network (Ackermann et al., 2007).

The basal ganglia (BG)

Similarly, the BG, known for their role in motor control, have been shown to participate in language processing. Price (2012) highlights that the BG are involved in the selection and initiation of language sequences, particularly in tasks that require the manipulation of phonological and syntactic information. Studies using PET and fMRI have demonstrated BG activation during language production and comprehension, suggesting their involvement in both articulatory processes and higher-order linguistic functions (Booth et al., 2007). The BG’s role in language is particularly evident in individuals with Parkinson's disease (PD), who often exhibit speech and language deficits such as reduced verbal fluency and difficulties with complex sentence structures. Degeneration of dopaminergic neurons in the substantia nigra disrupts the BG’s regulation of motor control, leading to the characteristic motor symptoms of the disease (Obeso et al., 2008). These impairments highlight the basal ganglia's contribution to the procedural aspects of language, including the sequencing and timing of linguistic elements (P. Lieberman, 2002). Skipper (2017) also stressed the involvement of the basal ganglia in semantic processing.

Distributed network theory

This integration, occurring across multiple brain regions, demonstrates that language comprehension is a holistic process that relies on the interaction of various neural circuits. The distributed network theory suggests that specialised functions of brain regions emerge from the connections and communication with other regions, rather than being intrinsic to a single area (M. M. Mesulam, 1990). This allows regions to participate in multiple functions depending on the network dynamics and the regions they are interacting with (Sporns, 2012).

From this distributed perspective, understanding the neurobiology of language requires mapping how it emerges from the integrated functioning of the brain's intricate system-wide neural architecture across multiple interlinked hubs and networks (Friederici & Singer, 2015). This perspective suggests that the dual stream model, while robust, may need to account for more fluid and flexible neural mechanisms. As (Skipper & Willems, 2015) puts it: "Language tasks arise from aggregate dynamic properties of a coupled multi-region neural system. This dynamic cooperation, while loosely domain specialised, is anything but module specific."

Skipper emphasises that language is deeply interwoven with other domain-general systems like perception, attention, memory, and cognitive control, aligning with theories of embodied, grounded cognition (Barsalou, 2008). From this perspective, the neural basis of language cannot be isolated from the brain's vast interactive networks underlying conscious experience.

The emergence of conscious language experience

The intricate and interconnected nature of language processing in the brain raises a fundamental question: How does this distributed neural activity give rise to our conscious experience of language and thought? In other words, how does the brain's complex orchestration of linguistic information translate into our subjective awareness of language? This question lies at the heart of the ongoing exploration into the neurobiology of language and consciousness.

The Neurobiology of consciousness

Consciousness, the subjective experience of the world around us and ourselves, is a complex phenomenon that has puzzled philosophers and scientists for centuries. While the exact neural mechanisms underlying consciousness remain a mystery, neuroscientists are making significant progress in understanding the brain regions and networks involved. This section will explore some of the prominent theories and models of consciousness, the neural correlates of conscious experience, the role of language in shaping consciousness, and the neural underpinnings of altered states of consciousness (ASCs)..

Consciousness remains one of the most perplexing phenomena in neuroscience. How does the brain give rise to subjective experiences and a first-person perspective? Diverse theories have been proposed to account for the neurobiological mechanisms underlying conscious states, though thus far none fully explain the subjective experience.

The Global Workspace Theory

Proposed by (Baars, 1997), the Global Workspace Theory (GWT) suggests that consciousness arises from the integration of information across a distributed network of neurones. This theory likens the brain to a theatre, where the spotlight of attention illuminates specific information, making it accessible to various cognitive processes (Sitt et al., 2014). Empirical support for GWT comes from neuroimaging studies demonstrating widespread activation and connectivity across the brain during conscious perception, particularly involving fronto-parietal networks (Dehaene et al., 2011).

However, GWT has been criticised for its inability to explain the qualitative aspects of conscious experience, often referred to as "qualia". Critics argue that while GWT provides a robust framework for understanding the mechanisms of attention and information integration, it falls short in explaining why certain neural processes are experienced subjectively (Chalmers, 1997; Hohwy, 2013). Additionally, some researchers question the necessity of a “global workspace” for all conscious experiences, suggesting that localised neural processes might suffice for certain types of consciousness (Lamme, 2006).

Integrated Information Theory

Integrated Information Theory (IIT), developed by Giulio (Tononi, 2004) focuses on the intrinsic properties of neural networks. IIT posits that consciousness correlates with the brain's ability to integrate information, quantified by the measure 'Φ' (phi). Higher Φ values are indicative of greater consciousness. Empirical studies have shown that states of reduced consciousness, like sleep or anaesthesia, are associated with decreased functional connectivity and integration in the brain, supporting IIT (Casali et al., 2013).

However, IIT has also faced criticism for its complexity and the difficulty of empirically measuring Φ in practical settings. Some researchers argue that the theory's mathematical formulations are challenging to apply to real-world data, limiting its empirical validation (Macgregor, 2006).

Higher-Order Theories

Higher-Order Theories (HOT), championed by philosophers like David (D. Rosenthal, 2005), propose that consciousness arises from the brain's ability to represent its own mental states. A mental state becomes conscious when it is the object of a higher-order representation. In other words, for a person to be consciously aware of a thought or perception, there must be a second-order thought that takes the first-order mental state as its content (D. M. Rosenthal, 1993). Neuroimaging studies have shown that tasks requiring self-reflection and metacognition activate higher-level associative areas, such as the prefrontal cortex (PFC), supporting HOT (Fleming, 2020).

However, critics argue that higher-order thoughts might not be necessary for conscious experience and question the reliability of introspection as an indicator of consciousness. One critique is that it requires an additional layer of cognitive processing, which some argue is unnecessary for explaining consciousness. Critics suggest that first-order representations might be sufficient for conscious experience, challenging the need for higher-order thoughts (Lamme, 2010). Additionally, HOT has been criticised for its reliance on introspective access, which may not be a reliable indicator of conscious experience (Block, 2011; Schwitzgebel, 2008).

Predictive Coding Theory

Predictive Coding Theory, put forth by Karl (Friston, 2010), views consciousness as the brain's model of its environment, constantly updated through prediction and error correction. The brain generates predictions about incoming sensory information and updates these predictions based on actual inputs. Consciousness, in this view, arises from the brain's hierarchical prediction errors.

Predictive Coding Theory provides a unifying framework for understanding perception, cognition, and consciousness. It suggests that the brain operates as a Bayesian inference machine, constantly generating hypotheses about the world and refining these hypotheses through sensory feedback. This model emphasises the role of cortical hierarchies, where higher-level regions generate predictions and lower-level regions provide error signals. For example, fMRI studies have demonstrated that unexpected stimuli elicit stronger neural responses in areas such as the anterior cingulate cortex (ACC) and the insula, which are associated with processing prediction errors (Clark, 2013).

However, critics argue that predictive coding may not fully capture the richness of conscious experience, particularly its qualitative aspects. Critics suggest that additional mechanisms might be necessary to explain these aspects of consciousness, such as the subjective feel of sensory experiences (Hohwy, 2013).

While each theory offers valuable insights, a unified model of consciousness remains elusive. The intricate nature of the brain and the subjective nature of conscious experience make it challenging to identify a single mechanism responsible for generating consciousness. Nevertheless, ongoing research continues to shed light on the neural correlates and potential mechanisms underlying this fascinating phenomenon.

Neural correlates of consciousness

Neuroimaging studies show that conscious perception is linked to extensive metabolic activity across the fronto-parietal association cortices, rather than restricted to isolated areas of the brain (Vanhaudenhuyse et al., 2010). This distributed nature of consciousness mirrors findings in the study of language, where processing involves multiple brain regions working in concert. Just as no single brain area is solely responsible for language, consciousness appears to arise from a dynamic interplay of many brain areas. NCCs have been observed in diverse regions, suggesting that consciousness is not the product of any one location, but rather a global phenomenon involving the integration of sensory, cognitive, and emotional information across various neural networks.

Key Brain Regions

Prefrontal Cortex

The PFC, important for executive processing, plays a crucial role in higher-order cognitive functions such as decision-making, planning, and self-reflection (Cavanna & Trimble, 2006). It is also essential for maintaining and manipulating information in working memory, a key component of sustained conscious awareness (Miller & Cohen, 2001). Neuroimaging studies consistently show PFC activation during tasks requiring conscious control and monitoring of thought processes, supporting its involvement in conscious experience.

Posterior Parietal Cortex

The posterior parietal cortex (PPC) is associated with integrating sensory information and spatial awareness (Culham & Kanwisher, 2001). It is involved in directing attention and is activated during conscious perception and visuospatial processing. This region is particularly vital for the conscious experience of the external environment, as it integrates visual, auditory, and tactile information to create a coherent perceptual representation.

Dynamic Interplay and Global Integration

As stated above, it is important to note that the dynamic interplay between these regions, rather than the activity of any single region, is likely the key to understanding consciousness. Studies using techniques such as fMRI, electroencephalography (EEG), and magnetoencephalography (MEG) have revealed that conscious perception is associated with global brain integration, characterised by enhanced functional connectivity—the temporal correlations between neural activities in different brain regions (Greicius et al., 2003).

Frontoparietal Network

The frontoparietal network (FPN), comprising regions in the lateral prefrontal cortex (LPFC) and PPC (mentioned above), is a key network involved in attention, working memory, and decision-making—all crucial for conscious awareness (Arnsten et al., 2012; Boly et al., 2008; Koch et al., 2016). This network exhibits amplified functional connectivity (FC) and neural signal propagation during conscious perception compared to unconscious conditions (Bor & Seth, 2012).

Notably, direct stimulation of the prefrontal and parietal association cortices, as well as the STG, can trigger vivid conscious experiences and thought insertion (Stripeikyte et al., 2021). Conversely, lesions or dysfunction in this frontoparietal system are associated with impairments in conscious reportability and subjective awareness, even when sensory processing remains intact (Tsuchiya et al., 2015).

Default Mode Network (DMN)

The “Default Mode Network”, or DMN, which includes regions such as the MPC, PCC/precuneus, inferior parietal lobule, AG, and medial temporal areas, is typically active during rest and self-referential thought. These regions show heightened activity during resting state when compared to focusing on external tasks (Buckner et al., 2008; Raichle et al., 2001).

The DMN is implicated in internal mentation, such as daydreaming, introspection, and the “stream of consciousness” (Raichle, 2015). Disruptions to the DMN have been associated with ASCs like vegetative states (Lehembre et al., 2012).

Importantly, the DMN exhibits strong functional connectivity during normal wakeful rest, with its core hubs tightly integrated in an orchestrated network (Greicius et al., 2003). It has been proposed that this cohesive internal coupling within the DMN may underlie our ability to experience a continuous and unified stream of conscious thought and self-awareness, or a subjective "mental space" (Northoff et al., 2006).

Intriguingly, the DMN overlaps significantly with the set of cortical regions identified as showing heightened neural complexity and integrative dynamics during conscious experiences. This has led some researchers to theorise that the DMN may constitute a privileged network whose cohesive connectivity patterns and dynamical properties allow it to generate and maintain coherent conscious scenes (Barttfeld et al., 2015).

While its precise role in consciousness is still debated, the DMN represents a crucial neural system for understanding how the functional architecture and dynamics within distributed cortical networks may give rise to different conscious states and contents.

Thalamocortical System

While often overlooked, the thalamus, a relay station for sensory information, is increasingly recognised as playing an integral role in enabling conscious experience. As a central hub relaying information across cortical areas, the thalamus is proposed to facilitate the large-scale integration and information broadcasting thought to give rise to consciousness. Accompanied by the cortex, the outer layer of the brain responsible for higher cognitive functions, this system allows for conscious information accessibility loops (Alkire, 2008; Halassa, 2022). Disruptions to the thalamocortical system loops, such as during anaesthesia or deep sleep, lead to a loss of consciousness (Alkire, 2008; Ward, 2011).

Language and Consciousness: A Deep Interconnectedness

Although the exact nature of the link between language and consciousness has yet to be determined, the accumulating evidence points to a deep interconnectedness between the two.

This notion is rooted in philosophical discourse, with thinkers like Bertrand Russell (1921) saying, “A desire is conscious when we have told ourselves that we have it,” suggesting that desires become conscious when articulated (Parkinson, 1970). Jean Piaget (1926), a renowned developmental psychologist, proposed that thought becomes conscious only through communication, stating, "Thought becomes conscious to the degree to which the child is able to communicate it” (Piaget, 1952). Gilbert Ryle (1949) further challenged the Cartesian dualism theory of Renault (Chapter 1.1), specifically the notion of a "ghost in the machine" – a separate mind or soul inhabiting the body (Ryle, 2009). He argued that language and conscious experience are different facets of behaviour and dispositions, rather than distinct entities, stating "the mythical separation of mind and body is reflected in the doctrine that minds or souls can become temporarily dissociated from bodies."

In the modern era, with our deepening knowledge of neuroscience, how do we reconcile these historical perspectives with the intricate workings of the brain? Does language merely reflect our conscious thoughts, or does it actively shape and mould our awareness? Emerging research suggests that the answer may lie somewhere in between. Daniel Dennett, a prominent philosopher and cognitive scientist, argued that language plays a crucial role in the overall emergence of human consciousness. In his book "Consciousness Explained," Dennett posited that our ability to use language to create narratives about ourselves and our experiences is what gives rise to our sense of self and subjective awareness (Dennett & Dennett, 1993). Therefore, language appears to play a pivotal role not only in our ability to introspect or articulate our thoughts, but also in constructing a coherent sense of self (Pinker, 1994; Vygotsky & Cole, 1978).

Inner-speech and self-reflection

The inner voice, that constant stream of verbal thoughts that accompanies our waking hours, may be a manifestation of this intricate relationship between language and consciousness. Many individuals experience this "inner voice", or inner speech, which represents a significant component of thought and self-reflection. This phenomenon has been proposed as a fundamental component of conscious thought and self-awareness. Inner speech mainly involves subvocal articulation, where individuals silently articulate words or sentences, often reflecting on past experiences, planning future actions, or engaging in self-talk (Morin, 2009; Vygotsky & Cole, 1978). It allows individuals to rehearse and manipulate information internally, facilitating complex cognitive tasks such as problem-solving and decision-making. Studies using fMRI have shown that inner speech activates similar brain regions to overt speech, including Broca and Wernicke's areas, the left IFG and STG, alongside the supplementary motor area (SMA). These findings suggest that inner speech involves a complex interplay between language production and comprehension areas, as well as motor planning regions (Alderson-Day & Fernyhough, 2015; Geva et al., 2011; Hurlburt et al., 2016; Shergill et al., 2002).

Embodied cognition

The theory of embodied cognition has gained traction in recent years, challenging traditional views of language as an abstract, amodal system. According to this perspective, language is deeply rooted in our sensorimotor experiences (Meteyard et al., 2012; Pulvermüller, 2013; Vigliocco et al., 2014) -- the way we use language is shaped by the way we interact with the world (Barsalou, 2008; Lakoff & Johnson, 1980). When we process language, we engage in a form of mental simulation, activating the same neural circuits involved in actual perception, action, and emotion (Barsalou, 2008; Damasio, 1989; Glenberg & Kaschak, 2002). From this view, language does not merely re-describe the world but constitutes a form of embodied, consciously re-experienced simulation. For instance, if one reads about grasping an apple, the same neural circuits that are actually involved in grasping said object will be activated, alongside multisensory representations of how an apple looks and feels, allowing us to "feel" the meaning of words and connect them to our own bodily experiences.

Neuroimaging and behavioural studies support these ideas (Gallese & Lakoff, 2005). Brain regions involved in perception and action become active during the comprehension of semantically related language (Hauk et al., 2004). Additionally, sensorimotor interference can impair performance on language tasks that require the simulation of the interfered modality (Glenberg et al., 2008). These findings suggest that language comprehension involves simulating described situations by reactivating sensory and motor information, which is closely tied to our conscious perception and awareness (Damasio, 1989).

Crucially, these simulated experiences are thought to share mechanisms with - and ultimately ground - our conscious perception and awareness itself (Barsalou, 2008; Damasio, 1989). From this perspective, language's ability to flexibly combine elements may play a central role in shaping how we actively build our conscious experiences (Overgaard et al., 2006). By allowing us to integrate and communicate across different sensory and cognitive domains, language helps create the mental representations that enable us to construct and simulate complex conscious scenes.

The implications of embodied cognition for the intersection of language and consciousness are significant. If our language and conceptual knowledge are indeed grounded in embodied experiences, then our conscious experiences and perceptions may also be shaped by these embodied representations. However, if our understanding of the world is fundamentally shaped by our bodily experiences, how do we transform these experiences into a coherent sense of self? The answer might lie in the power of language and the narratives we construct about our lives.

Narrative self

Beyond shaping individual experiences, language plays a pivotal role in constructing our sense of self and identity. The "narrative self" model posits that our conscious identity emerges from the linguistic ability to weave together our perceived events, mental states, and memories into a coherent autobiographical narrative. Through the stories we tell about ourselves and our lives, we create a coherent sense of self that persists over time (Dennett & Dennett, 1993). This narrative self is essentially a linguistic representation of our identity, shaped by social interactions and cultural context.

Linguist and cognitive scientist, Ray Jackendoff, suggests that linguistic abilities enable humans to become conscious of their own mental states and to think about their thoughts and experiences (Jackendoff, 2007; Perlovsky, 2009). Neuroimaging studies have found extensive overlap between language networks and the DMN (Buckner & Carroll, 2007). Hubs like the MPC are critical for integrating self-schemas into a coherent personal narrative. Damage to language hubs, i.e. lesions, like the left inferior frontal regions can also produce striking impairments in conscious self-monitoring and meta-representational skills (Shallice et al., 2008), as seen in conditions like schizophrenia and autism (Berkovich-Ohana et al., 2012; Fein, 2010). This overlap indicates that inner speech and language processing are deeply involved in conscious introspection and meta-awareness.

Taken together, these findings and theories suggest an intimate relationship whereby linguistic processes shape and potentially constitute key dimensions of human consciousness, from the embodied simulation of perceptual experiences to the construction of self-models and subjective identity over time. As eloquently stated by Dennett (1991), our human minds are a product of an "open-ended representational system" where language is the "culminating achievement." This perspective highlights the integral role of language in enabling our richly embodied, self-aware conscious experiences.

Beyond Narrative: Language as a Constitutive Force

While the narrative self model emphasises the role of language in constructing self-identity, the influence of language extends beyond personal narratives. Linguistic processes, particularly inner speech and embodied simulation, are not merely reflective of conscious experience but actively shape and even constitute key dimensions of it.

Research suggests that inner speech plays a crucial role in cognitive processes like planning, problem-solving, and self-regulation (Morin, 2009). Moreover, the activation of similar brain regions during inner and overt speech highlights the shared neural substrates underlying these linguistic processes (Alderson-Day & Fernyhough, 2015). Embodied cognition theories further underscore the constitutive role of language in shaping consciousness (Barsalou, 2008); (Revonsuo, 2006).

Our attention and focus can even affect how we understand and produce language (Dehaene & Naccache, 2001). Therefore, ASCs provide a unique perspective on the flexibility and adaptability of the human mind. These states, which can be induced through various means such as sleep, meditation, and psychoactive substances, reveal the dynamic nature of consciousness and its susceptibility to external and internal influences.

Altered states of consciousness and their neural underpinnings

ASCs are experiences that differ significantly from ordinary waking consciousness. These states, such as sleep, dreaming, and meditation, can be induced by drugs, brain stimulation, or certain practices. Studying these altered states provide insights into the neural basis of consciousness (R. Carhart-Harris & Nutt, 2014; Northoff et al., 2010; Zeidan & Vago, 2016).

Sleep

Sleep, a naturally occurring ASC, is characterised by distinct stages, including rapid eye movement (REM) and non-REM sleep. Neuroimaging studies have shown that during REM sleep, brain activity patterns resemble wakefulness, with increased activation in the limbic system (involved in emotions) and decreased activity in the PFC (involved in executive functions) (Pace-Schott & Hobson, 2002), and this phase is closely associated to vivid dreaming. This shift in neural activity may explain the emotional and often illogical nature of dreams. Notably, the linguistic content of dreams, often characterised by bizarre narratives and nonsensical dialogues, reflects the ASC and the brain's unique mode of processing information during sleep.

Meditation

Meditation practices, such as mindfulness meditation, can induce ASCs characterised by focused attention and heightened awareness. Neuroimaging studies have revealed distinct patterns of brain activity associated with different meditation practices, including changes in the DMN, attentional networks, and regions involved in self-referential processing (Fox et al., 2016; Tang et al., 2015). In addition, long-term meditation practitioners exhibit increased cortical thickness in areas related to attention and sensory processing (Lazar et al., 2005). Interestingly, language plays a crucial role in guiding and maintaining attention during meditation, as practitioners often use mantras or focus on specific phrases to anchor their awareness.

Hypnosis

Hypnosis, an ASC characterised by increased suggestibility and focused attention, involves a dissociation between different cognitive processes. This dissociation can lead to changes in perception, memory, and behaviour. Neuroimaging studies have implicated the anterior ACC, PFC, and thalamus in mediating the effects of hypnosis on consciousness (Halligan & Oakley, 2013). The power of suggestion during hypnosis, often delivered through language, highlights the profound influence of linguistic cues on our conscious experiences.

Brain injuries

Injuries to the thalamus can lead to profound disruptions in consciousness, resulting in conditions such as coma or persistent vegetative states (Laureys & Schiff, 2012; Schiff, 2010).

Similarly, traumatic brain injuries (TBIs) can lead to disorders of consciousness, where patients may fluctuate between states of minimal awareness and complete unresponsiveness.

Perhaps most strikingly, brain injuries offer a unique perspective on the relationship between language and consciousness. These cases often involve disruptions in language networks, leading to impairments in communication, self-awareness, and the ability to construct coherent narratives.

Psychedelics

Among the most intriguing of ASCs are those induced by classical psychedelics. ‘Classic’ serotonergic psychedelics such as psilocybin (found in “magic mushrooms”), lysergic acid diethylamide (LSD), and N,N-dimethyltryptamine (DMT), are a class of substances that profoundly alter perception, cognition, and conscious experience. Their effects are characterised by changes in sensory perception, altered sense of time and space, synesthesia, ego dissolution, and mystical or spiritual experiences. Thus, understanding the neural mechanisms underlying these states can provide further valuable insights into the nature of consciousness and its relationship with language.

Psychedelics and the Brain

The striking similarities between experiences of brain damage and psychedelic states provide a unique window into the workings of the conscious mind. Both conditions can disrupt normal neural pathways and lead to heightened, altered states of awareness. Research has shown that psychedelics can reduce the activity of the DMN, leading to a dissolution of the ego and a sense of oneness with the universe (R. L. Carhart-Harris et al., 2014). Similarly, damage to the DMN from brain injuries can result in a diminished sense of self and altered perception of reality.

A study by (R. L. Carhart-Harris et al., 2012) demonstrated that psilocybin decreases blood flow to key areas of the DMN, such as the MPC and PCC. These changes are associated with the intense subjective experiences of ego dissolution and altered perception, paralleling the disruptions seen in brain injury patients.

Quotes from individuals who have undergone brain injuries often also mirror experiences similar to those reported by users of psychedelics, such as altered perceptions of time and space, enhanced emotional experiences, and a sense of interconnectedness with the environment. For example, one patient described their experience post-injury as "living in a fog, where the edges of reality were blurred and constantly shifting" (Turner et al., 2014).

In both cases, there seems to be a disruption of the normal functioning of the neural networks that support our sense of self and our ability to integrate information across different sensory modalities. This disruption can lead to a profound change in the way we experience the world and ourselves, often accompanied by a sense of ineffability and a difficulty in translating the experience into language.

A case study comparing a near-death experience (NDE) with a psychedelic experience induced by 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) revealed significant similarities. Both experiences involved transcendence of time and space, ego dissolution, and a sense of cosmic unity. However, unique themes such as life review and encounters with deceased individuals were more prominent in NDEs, suggesting that while there are commonalities, there are also distinct elements unique to each type of experience (Michael et al., 2023).

Changes Induced by Psychedelics

Furthermore, psychedelics can cause many other conscious changes, such as:

- Altered perception: Psychedelics can alter our perception of the world around us, making us see, hear, and feel things differently. This can include hallucinations, where we see or hear things that are not there, and synesthesia, where one sense is experienced through another (e.g., hearing colours) (R. L. Carhart-Harris, Muthukumaraswamy, et al., 2016).
- Changes in mood and emotion: Psychedelics can also cause changes in mood and emotion, ranging from euphoria to anxiety and fear (Griffiths et al., 2006).
- Ego dissolution: One of the most common effects of psychedelics is ego dissolution, the temporary breakdown of the sense of self. From a firsthand perspective, the typical sense of being a single, coherent "I" can dissolve, replaced by kaleidoscopic flows of imagery and ephemeral self-boundary dissolution. Language abilities like inner speech often feel profoundly disrupted as well (Lebedev et al., 2015).
- Mystical experiences: Some people who take psychedelics report having mystical experiences, which are characterised by feelings of ineffability, peace, and unity (Griffiths et al., 2006).

Neuroplasticity

Neuroplasticity refers to the brain's ability to change and adapt in response to experiences, learning, and environmental factors. Recent research suggests that psychedelics may promote neuroplasticity, potentially contributing to their aforementioned therapeutic effects and their ability to induce lasting changes in brain function and behaviour (R. L. Carhart-Harris & Nutt, 2017).

Dendritic Growth and Synaptogenesis

Studies have demonstrated that psychedelics can promote dendritic growth and synaptogenesis, the formation of new synapses between neurones. A seminal study by (Ly et al., 2018) found that psychedelics such as LSD and psilocybin increase the density of dendritic spines in cortical neurons, which are tiny protrusions involved in synaptic transmission. This increase in dendritic spine density is associated with improved synaptic strength and plasticity, potentially enhancing cognitive flexibility and resilience against stress. Similarly, (Savalia et al., 2021) demonstrated that psilocybin promoted the growth of new neurones (neurogenesis) and increased dendritic complexity in the mouse hippocampus, a brain region involved in learning and memory (Catlow et al., 2013).

Psychedelics have also been shown to modulate functional plasticity, which involves changes in the strength and efficiency of synaptic transmission between neurones (Vollenweider & Kometer, 2010). For example, (Hibicke et al., 2020) found that a single dose of psilocybin enhanced long-term potentiation (LTP), a form of synaptic plasticity. (R. L. Carhart-Harris et al., 2017) found that psilocybin administration resulted in increased FC and structural changes in brain regions associated with emotion regulation and self-referential thought. These findings suggest that psychedelics can induce lasting changes in brain structure and function.

These findings also suggest that psychedelics may promote structural plasticity by enhancing the growth and connectivity of neurones, which could contribute to their therapeutic effects and their ability to induce lasting changes in brain function.

Enhanced Cortical Connectivity

Neuroimaging studies reveal that psychedelics can enhance cortical connectivity, facilitating communication between different brain regions. This enhanced connectivity is particularly notable in the DMN and the salience network (SN), which helps to detect and filter important stimuli (Petri et al., 2014). Increased connectivity may support the reorganisation of neural circuits, allowing for new patterns of thought and behaviour to emerge.

Such promotion of neuroplastic processes could potentially facilitate reorganisation and updating of brain circuitry - a mechanism proposed to underlie the therapeutic effects of psychedelics in conditions like depression, anxiety, and addiction (Yaden & Griffiths, 2021). The heightened plasticity may open a "revitalising neurological window" allowing dysfunctional patterns to be disrupted and adaptive modes of processing reinforced.

In the context of consciousness, psychedelics could be inducing long-term reorganisation of the distributed neural networks and oscillatory dynamics that give rise to certain characteristics of subjective awareness and cognition. Some have even speculated that psychedelic neuroplasticity could potentially expand the computational capacities and richness of conscious experiences (Timmermann et al., 2023).

(Swanson, 2018) suggests that psychedelics may work by a combination of enhancing neural plasticity and promoting synaptic growth. This increased plasticity may allow for the rewiring of neural circuits and the formation of new connections, potentially leading to long-lasting changes in brain function and behaviour.

While still an area requiring more research, the emerging evidence of psychedelic neuroplasticity suggests these compounds may have unique potential, not just for disrupting normal states of consciousness, but also for reprogramming brain dynamics in ways that promote lasting changes in perception, cognition and well-being.

Understanding how psychedelics can facilitate lasting changes in brain structure and connectivity provides a foundation for their use in treating a variety of mental health conditions.

Molecular Mechanisms of Psychedelic Action

The exact neurobiological mechanisms by which psychedelics produce these effects are still not fully understood. However, research suggests that they may work by interacting with the serotonin systems in the brain.

5HT2A Receptor Activation

Serotonin (5-HT) is a neurotransmitter that is involved in a variety of functions, including mood regulation, perception, and cognition. Psychedelics are believed to bind to 5-HT receptors in the brain, which can alter the way that nerve cells communicate with each other.

A central player in this process is the 5-HT 2A receptor (5-HT2A), a subtype of 5-HT receptor, which is densely expressed across the brain (Nichols, 2016), primarily in higher-order cortical regions like the prefrontal, insular and ACC. This ACC / fronto-parietal nexus is proposed to play a pivotal role in integrating internal narrative/self models with perception. By binding to and activating the 5-HT2A receptor, a cascade of neural events that lead to the characteristic ASCs is triggered (Vollenweider & Kometer, 2010). These include the activation of the mammalian target of rapamycin (mTOR) pathway, a key regulator of protein synthesis and synaptic plasticity (Olson, 2018), which profoundly alters the way different regions communicate and interact.

Increased Glutamate Release

Psychedelics can enhance the release of glutamate, the brain's primary excitatory neurotransmitter. Glutamate plays a crucial role in synaptic plasticity and learning, and its increased release may contribute to the neuroplastic effects of psychedelics (Muschamp et al., 2014).

BDNF Upregulation

Brain-derived neurotrophic factor (BDNF) is a protein that promotes the survival and growth of neurones and plays a vital role in neuroplasticity. Psychedelics have been shown to increase BDNF levels in the brain, potentially contributing to their long-lasting therapeutic effects (Ly et al., 2018).

Inflammatory Modulation

Some evidence suggests that psychedelics may modulate inflammatory processes in the brain, which can indirectly promote neuroplasticity. By reducing inflammation, psychedelics may create a more favourable environment for neuronal growth and repair (Flanagan & Nichols, 2018).

Theories of psychedelic action

Several theories have been proposed to explain the mechanisms through which psychedelics produce their profound effects on consciousness. Here are some of the leading theories, more generally:

Modulation of the PFC

Psychedelics affect activity in the PFC, as mentioned, a key brain region associated with consciousness, and involved in higher-order cognitive functions, executive control, and self-awareness. This modulation may contribute to the cognitive and perceptual changes experienced during psychedelic states (R. L. Carhart-Harris et al., 2014; Vollenweider & Preller, 2020). Neuroimaging studies of TBI patients have also shown disrupted connectivity in fronto-parietal networks, as discussed in the prior section, similar to the effects observed during certain phases of psychedelic experiences (Boly et al., 2013).

DMN Modulation

Psychedelics have been shown to decrease activity in the DMN (described above). This disruption of the DMN may contribute to the experience of ego dissolution. The DMN's reduced connectivity under the influence of psychedelics then leads to a diminished sense of self and increased interconnectedness with the environment (R. L. Carhart-Harris et al., 2012; Palhano-Fontes et al., 2015).

Global Integration and Connectivity

Psychedelics enhance global connectivity across the brain, increasing communication between regions that are normally segregated. This increased connectivity may contribute to the dissolution of boundaries between self and others, the sense of unity with the universe, and the merging of sensory modalities (synaesthesia) often reported during psychedelic experiences. This global integration allows for a more unified and interconnected conscious experience (Tagliazucchi et al., 2014). Damage to the temporal lobes can trigger hallucinations, mystical experiences, and a sense of unity with the universe, similar to the effects reported by individuals using psychedelic substances (Ramachandran & Blakeslee, 1998). This convergence of experiences suggests a potential overlap in the neural mechanisms underlying both brain injury-induced and psychedelic-induced alterations in consciousness.

Frameworks of psychedelic action

Predictive Processing and Bayesian Brain

This framework posits that the brain operates by constantly generating predictions about the world and updating these predictions based on sensory input. Psychedelics are thought to disrupt these predictive processes, leading to a state of heightened sensory awareness and a loosening of the grip of prior expectations (Corlett et al., 2009). This model is supported by studies showing that psychedelics alter sensory perception and reduce the influence of prior knowledge on cognition.

REBUS (Relaxed Beliefs Under Psychedelics)

The REBUS model, proposed by (R. L. Carhart-Harris & Friston, 2019)), suggests that psychedelics relax the brain's priors or beliefs, making it more flexible and less constrained by previous learning and expectations. Normally, these predictions help to reduce uncertainty and guide our perception and behaviour. However, in some cases, these prior beliefs can become overly rigid or maladaptive, leading to mental health issues such as depression or addiction.

Psychedelics allow for a more free-flowing and less predictable stream of consciousness, which can lead to novel insights and perceptions, and results in the characteristic perceptual and cognitive changes associated with psychedelic states, such as ego dissolution and synesthesia. This relaxation of priors is thought to be mediated by the 5-HT2A receptor. The result is a more flexible and adaptable state of mind, characterised by increased neural plasticity, enhanced creativity, and a greater openness to new experiences and perspectives. According to this model, psychedelics reduce the influence of top-down processes, allowing bottom-up sensory input to dominate experience (R. L. Carhart-Harris & Friston, 2019).

Entropic Brain Hypothesis

This theory, also proposed by (R. L. Carhart-Harris et al., 2014), posits that the psychedelic state is characterised by increased entropy or disorder in the brain's neural activity. This heightened state of disorder allows for a breakdown of rigid cognitive and perceptual patterns, facilitating a state of consciousness that is more fluid and malleable. The increased neural entropy is thought to correlate with the intensity and richness of psychedelic experiences (R. L. Carhart-Harris et al., 2014). Higher neural entropy is associated with a richer, more diverse conscious experience, which may explain the heightened creativity and novel insights reported during psychedelic trips.

Cortical Desynchronisation

Psychedelics are believed to cause a desynchronisation of cortical activity, particularly in the alpha and beta frequency bands. This desynchronisation disrupts the brain's normal rhythmic oscillations, leading to altered sensory perception, heightened emotional arousal, and changes in attention and focus. This disruption of coordinated neural oscillations may contribute to the profound changes in consciousness experienced during psychedelic states (Muthukumaraswamy et al., 2013). For example, psychedelics have been found to reduce the rhythmic neural signal diversity associated with conscious states. Diminished oscillatory metastability could impair the brain's ability to maintain coherent trajectories separating signal and noise.

Thalamic Filtering Hypothesis

According to this theory, psychedelics reduce the filtering capacity of the thalamus. This reduction allows for an overload of sensory information reaching the conscious mind, contributing to the vivid perceptual alterations experienced under psychedelics (Vollenweider & Geyer, 2001). This theory suggests that psychedelics disrupt normal thalamocortical rhythms, leading to altered states of consciousness. As discussed previously in the chapter, the thalamus acts as a relay station, filtering and integrating sensory information before it reaches the cortex. By disrupting these rhythms, psychedelics may alter the flow of sensory and cognitive information, contributing to the unique subjective experiences associated with these substances (Llinás et al., 1999).

Activation of the Claustrum

The claustrum theory, proposed by (Stiefel et al., 2014) and (Crick & Koch, 2005), suggests that the claustrum, a thin, sheet-like structure located deep within the brain, plays a crucial role in the integration of conscious experience. The claustrum has widespread reciprocal connections with various cortical regions, including the prefrontal, parietal, temporal, and occipital cortices, as well as with subcortical structures such as the thalamus and amygdala. According to this theory, the claustrum acts as a central hub or "conductor" that coordinates and synchronises the activity of different brain regions, enabling the integration of multisensory information into a unified conscious experience.

Psychedelics have been shown to increase activity in the claustrum, which may play a role in the altered conscious states induced by these substances (Vollenweider & Geyer, 2001). The claustrum theory is supported by several lines of evidence, including the high density of 5-HT2A receptors in the claustrum and the altered functional connectivity of the claustrum during psychedelic states (Barrett et al., 2020).

Integrated Information Theory (IIT)

As previously discussed, IIT proposes that consciousness arises from the brain's capacity to integrate information. Psychedelics may increase the brain's integrative capacity, leading to a more unified and interconnected conscious experience (Tagliazucchi et al., 2014).

Limitations and unanswered questions

Each of the above theories offers valuable insights into the mechanisms of psychedelic action, but they also have their limitations and challenges. For instance, while the DMN is a major focus of most research and the aforementioned theories, psychedelics have been shown to affect other brain networks (Muthukumaraswamy et al., 2013). The SN, responsible for detecting and orienting to relevant stimuli, may be involved in the heightened sensory perception and emotional intensity often experienced during psychedelic trips.

Most of the presented theories are also very simplistic and nonspecific and may not fully explain the complex emotional and spiritual experiences often reported during psychedelic states or their long-term impact on cognition and well-being.

In essence, studying these druggedly "dissolved" states could expose just how fundamentally language capabilities are woven into the dynamic spatiotemporal patterns generating our ordinary conscious phenomenology. By framing altered psychedelic states as disruptions to the hierarchical integration and narrative-binding processes proposed to ground self-conscious experience, this transition sets the stage to explore how these compounds can shed light on the neurobiological links between higher cognitive faculties like language and the mechanisms underlying subjective consciousness itself. It lays the groundwork for a focused examination of how psychedelics specifically impact language processing and higher-order self-referential cognition.

Psychedelics and language

The intersection of psychedelics, neuroplasticity, and language processing is particularly intriguing. As psychedelics promote the growth of new neural connections and enhance cortical connectivity, they may also impact the neural circuits involved in language and communication. This potential influence on language-related brain regions opens up new avenues for understanding how psychedelics affect linguistic capabilities and consciousness.

While the effects of psychedelics on language processing have been relatively understudied, some research suggests that these substances can alter semantic processing, metaphor comprehension, and language-related cognitive control (Sanz et al., 2022). For example, studies have found that psychedelics can enhance the comprehension of metaphors and facilitate more abstract, associative thinking. Additionally, psychedelics may impact language production and the ability to engage in certain cognitive tasks involving language (Fadiman, 2011). In fact, in some cases, psychedelics can lead to mild impairments in syntax and grammar, resulting in more fragmented or nonsensical speech (Carhart-Harris et al., 2014). This may reflect a temporary loosening of the usual constraints on language processing. These alterations in language processing may be related to the profound changes in conscious experience induced by psychedelics, as well as their effects on brain regions and networks involved in both language and consciousness.

Research has shown that psychedelics can significantly impact language processing. Users often report changes in the fluency, coherence, and structure of their speech and thoughts. These changes can manifest as an enhanced ability to make novel connections between concepts, often described as "hyper-associative thinking," or as difficulties in articulating thoughts coherently (Gouzoulis-Mayfrank et al., 1998; Spitzer et al., 1996). Participants often describe experiencing a greater flow of thoughts and ideas, as well as a heightened ability to express themselves verbally.

Neuroimaging studies support these subjective reports by showing that psychedelics affect brain regions involved in language production and comprehension. For instance, psilocybin has been shown to increase connectivity between the PFC and the language-processing regions of the brain, potentially facilitating more creative and less constrained use of language (R. L. Carhart-Harris et al., 2012).

Psychedelics can also disrupt semantic networks, leading to unusual associations between words and concepts (Spitzer et al., 1996). This may contribute to the feeling of "expanded consciousness" and novel insights often reported during psychedelic experiences. Additionally, many individuals report that their inner speech becomes more intense, vivid, and emotionally charged during psychedelic experiences (Shanon, 2002). This heightened internal monologue can lead to deep introspection, self-reflection, and insights into personal beliefs and values.

The content of inner speech can also be altered under the influence of psychedelics. Individuals may experience a shift from their usual self-referential thoughts to more universal or transcendental themes (Carhart-Harris et al., 2014). In addition, the narrative structure of inner speech may become more fragmented or nonlinear. The loss of this linguistically-mediated self-modelling may underlie the fragmentation of personal identity and ego dissolution so commonly reported. Without inner speech providing a coherent subjective storyline, the boundaries between self and world break down into kaleidoscopic phenomenal fluxes.

Due to this, the narrative self, which relies heavily on language to construct and maintain personal identity, can be profoundly affected by psychedelics. The dissolution of the ego and the altered sense of self often reported during psychedelic experiences can disrupt the continuity of personal narratives. Users may experience a sense of detachment from their usual self-concept and a re-evaluation of their life stories (R. L. Carhart-Harris & Friston, 2019).

These experiences can lead to long-term changes in how individuals perceive themselves and their place in the world. By breaking down established narrative structures, psychedelics may facilitate the integration of new insights and perspectives, contributing to personal growth and therapeutic outcomes (Griffiths et al., 2006).

This breakdown of self-coherence may directly result from dysregulating the neural dynamics that allow the DMN to integrate representations of episodic memories and cognitive operations into an overarching, temporally stable narrative frame. Without the DMN providing this binding "narrative matrix", personal history and prospective modelling become dissociated into disjoined phenomenal fragments.

Similarly, the functional decoupling of the DMN from other large-scale networks like the frontoparietal control system appears to degrade processes like cognitive control, working memory and metacognitive self-monitoring. This disruption to the DMN's integration with executive networks may impair our ability to actively construct and metacognitively regulate the symbolic, linguistically-mediated self-models that we experience as the locus of our conscious identity.

Essentially, by disrupting processes like inner speech, autobiographical narration, conceptual abstraction and linguistic situation-modelling, psychedelics may be compromising our ability to actively generate and constrain the types of higher-order symbolic/linguistic representations that theoretical accounts propose as foundational for instantiating our normal waking conscious experiences as integrated multimodal scene simulations.

As (Lupyan & Clark, 2015) argue, by "removing language from perception" psychedelics provide a glimpse of an unconstrained, less conceptualised experiential field - exposing just how fundamentally language may help structure our typical phenomenological world-models and stream of subjective awareness.

Psychedelics offer a unique tool for exploring the relationship between language and consciousness. By perturbing normal language processing and disrupting habitual thought patterns, they can reveal the underlying neural mechanisms that connect language to conscious experience. Understanding how psychedelics modulate language and inner speech could inform the development of new therapeutic approaches for conditions characterised by rigid thought patterns and negative self-talk, such as depression and anxiety.

After a psychedelic experience, language plays a crucial role in integrating and making sense of the ASCs. Through verbalising their experiences, individuals can process and integrate the insights gained during the psychedelic state into their ongoing narrative self. This process is often facilitated in therapeutic settings, where guided discussions help individuals articulate and understand their experiences (Watts et al., 2017).

Psychedelic assisted psychotherapy (PAP)

Psychedelics have been used for spiritual and religious purposes for centuries, and they are currently being investigated for their potential therapeutic applications in treating mental health conditions such as anxiety, depression, and addiction.

The neuroplastic effects of psychedelics hold immense therapeutic potential. By promoting the growth and reorganisation of neural circuits, psychedelics may be able to "reset" maladaptive patterns of thought and behaviour that contribute to various mental health conditions. Therefore, psychedelic-assisted therapy could enhance therapeutic outcomes when combined with other interventions, such as psychotherapy or language-based interventions (R. L. Carhart-Harris & Goodwin, 2017). One instance is psychedelic assisted psychotherapy (PAP) (Nutt et al., 2020).

In PAP models, patients undergo structured psychotherapeutic support and preparation before experiencing a single or small number of psychedelic sessions in controlled settings. The acute psychedelic experience is intended to facilitate insights, emotional processing and cognitive/perspective shifts that can then be integrated through subsequent non-drug psychotherapy (Reiff et al., 2021).

Proponents theorise that the neuroplastic properties of psychedelics may help "open a window" of heightened plasticity, allowing dysfunctional patterns of thought, behaviour and brain connectivity to be disrupted. The psychedelic experience itself can provide opportunities for revisiting memories, fears and maladaptive cognitive schemas from new perspectives.

When coupled with psychotherapeutic support, the insights and emotions elicited by psychedelics could become encoded into lasting neuroplastic changes - strengthening more adaptive cognitive strategies, belief systems and neural pathways (Ly et al., 2018). The ASCs may help patients gain psychological flexibility and revisit past traumas from a more detached, integrated psychological space. Neuroimaging data suggests psychedelic therapy leads to changes in brain connectivity patterns, particularly in networks like the DMN (Daws et al., 2022).

While still an emerging field requiring further research, PAP models aim to strategically leverage the neuroplastic, perspective-shifting and consciousness-expanding properties of these compounds to help reshape neural circuitry and cognition in beneficial ways.

Alongside showing promise in enhancing general mindfulness and self-awareness (Griffiths et al., 2018), PAP could offer future treatments for:

Depression and Anxiety

Early clinical trials of PAP for treatment-resistant depression, cancer-related distress and other conditions have shown promising results (R. L. Carhart-Harris, Bolstridge, et al., 2016); (R. L. Carhart-Harris et al., 2018; M. T. Davis et al., 2021). Studies have demonstrated that psychedelics, such as psilocybin and ayahuasca, can produce rapid and sustained reductions in depressive and anxiety symptoms. These effects are thought to be mediated by enhanced neuroplasticity, increased emotional processing, and a reduction in the activity of the DMN (R. L. Carhart-Harris, Muthukumaraswamy, et al., 2016; Palhano-Fontes et al., 2019). This reduction in DMN activity, coupled with increased connectivity between other brain regions, may allow for greater emotional openness, novel perspectives, and the ability to break free from negative thought patterns (R. L. Carhart-Harris et al., 2012; R. L. Carhart-Harris, Muthukumaraswamy, et al., 2016; Rhead, 2018).

Post-traumatic Stress Disorder (PTSD)

Psychedelics are also being investigated for their potential to treat PTSD. The enhanced neuroplasticity induced by psychedelics may help patients reprocess traumatic memories and integrate them into their narratives in a less distressing manner, allowing them to develop new coping mechanisms and contributing to long-term recovery. This process can be facilitated by the supportive context of psychotherapy, where patients can explore and reframe their traumatic experiences (Mithoefer et al., 2016); (Mithoefer et al., 2019).

Addiction

Psychedelics have been investigated for their potential to treat addiction to substances such as alcohol, nicotine, and opioids. Studies have found that psychedelics can reduce cravings and increase abstinence rates, potentially through mechanisms involving enhanced neuroplasticity and the disruption of maladaptive neural circuits associated with addiction (Bogenschutz & Johnson, 2016). Psychedelic therapy may promote neuroplasticity in brain regions involved in reward and motivation, helping individuals to overcome entrenched addictive behaviours and develop new, healthier habits (Bogenschutz & Johnson, 2016). Psychedelics may help individuals to "rewire" their brains and break free from ingrained habits and cravings (Johnson et al., 2014). By promoting neuroplasticity, psychedelics may facilitate the formation of new neural pathways that support healthier behaviours and thought patterns.

Similarly, in a study of psilocybin-assisted treatment for tobacco addiction, (Noorani et al., 2018) found that psilocybin led to significant increases in smoking abstinence rates, which were associated with changes in brain connectivity and the strengthening of connections between the DMN and the executive control network. These findings suggest that the neuroplastic effects of psychedelics may play a role in their ability to facilitate the breaking of addictive behaviours and the learning of new, healthier habits.

By promoting the growth of new neural connections and enhancing the brain's flexibility, psychedelics can facilitate profound and lasting changes in mental health. This emerging field of research holds promise for developing novel treatments for a range of psychiatric disorders, offering hope for individuals who have not responded to traditional therapies.

While the therapeutic potential of psychedelics is promising, it's important to proceed with caution and conduct rigorous research to ensure the safety and efficacy of these treatments since psychedelic substances can also be associated with risks, such as psychological distress and hallucinating persisting perceptual disorders (HPPD). Therefore, research must be conducted in a safe and controlled setting.

Our future research, therefore, aims to:

- Elucidate the precise mechanisms underlying psychedelic-induced neuroplasticity.
- Explore the potential of combining psychedelics with other therapies, such as psychotherapy.
- Investigate the long-term effects of psychedelic-induced neuroplasticity on brain function and behaviour.

One influential perspective in this domain is Jeremy Skipper's HOLISTIC framework, which proposes an integrated model whereby higher-order language capacities and inner speech processes play a constitutive role in generating conscious experiences themselves.

The Higher Order Language and Inner Speech to "I" Consciousness (HOLISTIC) Model

The HOLISTIC model (Higher Order Language and Inner Speech to "I" Consciousness) proposed by Jeremy Skipper posits that inner speech and language processing are deeply integrated with conscious experience and self-awareness (Skipper & Willems, 2015). According to this model, language processing is not confined to dedicated "language regions" but rather involves distributed cortical networks that contribute to the emergence of consciousness. Rather than isolatable faculties, (Skipper, 2014) argues that language and consciousness are interwoven, with linguistic processes like inner speech providing core representational codes and mechanisms that allow conscious scenes and selfhood to emerge.

Specifically, within this framework, the 'language network' should be understood as including not only traditional language areas like Broca's area and Wernicke's area, but also other key regions. These include the anterior superior temporal gyrus (aSTG), crucial for semantic processing; the inferior parietal lobule (IPL), involved in integrating phonological and semantic information; and prefrontal regions like the dorsolateral prefrontal cortex (dlPFC), contributing to higher-order cognitive control and integration of language with other cognitive functions. Furthermore, given the model's emphasis on inner speech and consciousness, regions supporting these functions, such as the medial prefrontal cortex (mPFC) and precuneus, should also be considered part of this extended language network. Additionally, the language network extends to other areas such as the angular gyrus and supramarginal gyrus, which are implicated in semantic processing and the integration of sensory information (Blank et al., 2016; Jeong et al., 2014). The involvement of the premotor cortex and inferior parietal lobule further illustrates the complexity of the language network, as these regions contribute to both the planning and execution of speech as well as the processing of linguistic stimuli (Jeong et al., 2014; Sul et al., 2016). The basal ganglia, cerebellum, and the dorsal and ventral pathways could also be included.This network, therefore, extends beyond the traditionally defined language areas and includes regions crucial for the integration of linguistic information with other cognitive processes, including those related to self-awareness and consciousness.

According to HOLISTIC, higher-order operations like constructing coherent situational models, projecting alternative hypothetical perspectives, and forming recursive meta-representations critically rely on language faculties. By iteratively integrating multimodal information into compressed symbolic descriptions, language allows us to generate and actively sculpt the types of rich simulated representations that comprise our stream of conscious experiences and reality-modelling (Skipper & Willems, 2015).

Skipper proposes that the medial and lateral frontal regions activated during tasks like story comprehension constitute a "descriptive situational integrator" that contextualises linguistic inputs into conscious narrative simulations. Meanwhile, the anterior temporal lobes are proposed semantic hubs supporting abstraction and inference about grounded conceptual representations.

Crucially, on this view conscious experiences do not arise from discrete modules like a "language centre" versus a "consciousness centre." Instead, Skipper theorises that consciousness emerges from the functional dynamics and connectivity across distributed cortical networks involved in perception, cognitive control, self-modelling, and language - with language processes playing a pivotal role in flexibly coordinating and compressing information into awareness (Skipper, 2014).

By framing higher-order linguistic capacities as integral and potentially constitutive processes for generating conscious experience, this perspective sheds light on the profound effects of psychedelics on consciousness observed in the research discussed above. The alterations in language processes under psychedelics, such as the dissolution of inner speech and self-narratives, may reflect a temporary disruption of the linguistic mechanisms that normally constrain and organise conscious experience.

Moreover, the neuroplastic impact of psychedelics on language networks and their connectivity with other cognitive systems, as described in the previous sections, may facilitate a fundamental rewiring of the neural representations and dynamics that give rise to conscious states. By inducing plasticity in the brain circuits underlying language-based cognition, psychedelics could enable a profound reorganisation of conscious experience itself.

From the HOLISTIC perspective, PAP may work by disrupting maladaptive language-based cognitive patterns and promoting the generation of more flexible and adaptive models of reality. The supportive context of psychotherapy can help guide the reorganisation of language processes and conscious experiences in a therapeutic direction, leading to lasting changes in thoughts, emotions, and behaviour. As such, the HOLISTIC theory suggests that targeting language-related mechanisms may be a key pathway through which psychedelics can induce transformative shifts in consciousness and well-being.

In conclusion, the HOLISTIC theory provides a unifying framework for understanding the intimate connections between language, consciousness, and the effects of psychedelics. It highlights the central role of language in shaping subjective experience and points to the therapeutic potential of harnessing psychedelic-induced neuroplasticity in language networks.

By emphasising the distributed nature of language processing and the crucial role of inner speech in self-reflection, the HOLISTIC theory offers valuable insights into the profound changes in consciousness induced by psychedelics. This theoretical perspective not only enhances our understanding of the neural mechanisms underlying these experiences but also highlights the potential for therapeutic applications of psychedelics in promoting cognitive flexibility and personal growth.

HOLISTIC vs REBUS

Although some might question the need for another model to explain the effects of psychedelic action, as stated above, none of the models mentioned prior explicitly discuss language and its contribution to not only the experience but the subjective effects overall. Since the REBUS model is most prominent and similar to the model proposed herein this thesis, differences must be addressed.

While both the REBUS and HOLISTIC models aim to explain the mechanisms of psychedelic experience, they differ in their overall focus and scope. For instance, Carhart-Harris' REBUS model posits that psychedelics induce a state where the brain's predictive coding mechanisms are relaxed, allowing for greater variability in conscious experience and a reduction in the precision of neurobiologically-encoded beliefs. This model is grounded in the Free Energy Principle, suggesting that psychedelics facilitate a more flexible and less constrained neural state, which can lead to novel insights and therapeutic outcomes by altering the brain's functional connectivity (Carhart-Harris & Friston, 2019; Safron et al., 2020; Zeifman et al., 2022). Although this model includes the whole-brain, it primarily emphasises the role of the DMN and its interaction with other brain regions in shaping subjective experience.

In contrast, Skipper's HOLISTIC model proposes a more language-oriented view, suggesting that psychedelics enhance communication between different levels of the brain's language system, ultimately leading to a heightened sense of self-awareness (Skipper et al., 2022). Skipper argues that language is not merely a tool for communication but is fundamentally intertwined with conscious experience, influencing how individuals perceive and interpret their thoughts and surroundings. This model challenges traditional localisationist views of language processing by highlighting the dynamic and context-dependent nature of language's relationship with consciousness (Skipper et al., 2024). Skipper's model suggests that inner speech production regions initiate the experience of feeling and hearing words, which then take on affective qualities through activation of associated sensory, motor, and emotional representations. In this view, cognition and language serve as scaffolds that organize and unify otherwise disparate neural activities, producing a coherent subjective experience. This perspective emphasises the role of narrative construction, semantic networks, and the social embedding of language in shaping conscious thought.

Thus, while both models address the complexities of consciousness, they do so from different angles: REBUS through the lens of neurodynamics and the disruption of top-down control and HOLISTIC through the lens of language and cognitive processing. Both offer valuable insights into the psychedelic experience, but they approach the phenomenon from different perspectives and highlight distinct neural mechanisms.

This thesis investigates the neural correlates of language processing, focusing on its relationship with wellbeing and the impact of DMT on language-related brain activity. The research builds on the HOLISTIC framework described above. Within this context, I explore two key questions:

1. How does the brain process different categories of wellbeing-related words, and how do these patterns relate to overall wellbeing?
2. How does DMT disrupt neural networks responsible for language processing, and what does this reveal about the role of language in shaping consciousness?

These questions are motivated by two streams of literature: first, studies demonstrating that language processing extends beyond traditional linguistic areas, integrating with networks involved in emotional regulation and self-referential cognition (Binder et al., 2009); and second, psychedelic research showing that substances like DMT alter connectivity in the DMN—a key system underlying self-awareness and internal thought processes (Carhart-Harris et al., 2014).

To address these questions, this thesis employs a combination of fMRI, predictive modeling using machine learning, and meta-analytic approaches to synthesise findings from psychedelic and ketamine studies. A central hypothesis is that wellbeing-related language engages a distributed neural network, and disruptions to this network under psychedelics lead to altered conscious experiences. By analysing fMRI data from the Naturalistic Neuroimaging Database (NNDb) and validating findings through the UNITy study, this research provides new insights into how language and psychedelics interact to shape cognition and subjective experience.

Thus, the research questions are motivated by the need to understand how these psychedelic-induced changes can inform our comprehension of both language and consciousness, particularly in the context of psychological wellbeing.

Overarching Hypotheses

In this thesis, we therefore hypothesise that:

1. Psychedelic substances induce alterations in consciousness by modulating neural activity across distributed brain networks, including those involved in language processing and self-referential thought.
2. Changes in language-related brain regions mediate the effects of psychedelics on conscious experience, facilitating novel cognitive and perceptual states through enhanced neuroplasticity and connectivity.
3. Psychedelic-induced neuroplasticity in language-related brain networks is a key mechanism underlying the therapeutic potential of these compounds for mental health and well-being.
4. Integrative theories such as Jeremy Skipper's HOLISTIC theory provide a comprehensive framework for understanding the complex interplay between language, consciousness, and neuroplasticity, elucidating how psychedelics can be leveraged for therapeutic purposes.

For each chapter, the hypotheses are as follows:

1. Chapter 2: Language-related neural processes serve as a fundamental mechanism through which psychedelics induce alterations in conscious experience and wellbeing. Psychedelics disrupt the neural integration of language, leading to altered self-referential cognition and shifts in conscious experience.
2. Chapter 3: Wellbeing-related word categories (cognitive, emotional, social, and etc) engage distinct yet overlapping neural networks, and the strength of these activations predicts subjective wellbeing.
3. Chapter 4: Neuroplastic changes induced by tryptamines, as measured by fMRI, can be predicted by language-based models of wellbeing. Psychedelic-induced neuroplasticity enhances cognitive and emotional flexibility, contributing to improved mental health outcomes, as measurable by changes in brain activity and language use.

By addressing these hypotheses, my thesis has the potential to advance our theoretical understanding of consciousness, inform the development of language-based diagnostic and therapeutic tools, and guide future research at the intersection of psychedelics, neuroplasticity, and mental health.

Thesis Overview

The thesis is arranged into three following chapters:

- **Chapter 2**: The Neurobiology of Language Partially Mediates Alterations in Conscious Experience Induced by Psychedelic Drugs. This section presents a meta-analysis of all existing neuroimaging studies on classic psychedelics and ketamine. It aims to elucidate the neural correlates of psychedelic experiences and investigate how changes in language-related brain regions contribute to the alterations in consciousness observed during these experiences. By examining the consistent patterns of neural activity and connectivity across multiple studies, this analysis will provide insights into the role of language processes in shaping the subjective effects of psychedelics. This section will provide empirical support for Hypotheses 1 and 2, demonstrating that psychedelics influence conscious states by affecting neural circuits involved in language processing.
- **Chapter 3**: Language-Based Predictive Modeling of Wellbeing in fMRI. This section involves training a predictive model to classify participants' wellbeing (low/high) based on linguistic features from fMRI data of participants watching a movie. The linguistic content

will be analysed to identify word categories (e.g., positive, negative, neutral) and used to train a machine learning model to predict wellbeing states. The model's performance and its implications for understanding the relationship between language use and wellbeing will be discussed. The findings will contribute to our understanding of the neural correlates of wellbeing and the potential of language-based modelling approaches. This section addresses Hypotheses 3 and 4 by demonstrating that well-being can be accurately predicted through language-based models, highlighting the relationship between language use, neural activity, and emotional states.

- **Chapter 4**: Understanding Neuroplasticity Induced by Tryptamines (UNITy Project)**.** Using data from the UNITy project, this section will apply the language-based well-being model developed in Chapter 3 to fMRI data collected from participants before and after DMT administration. The goal is to predict changes in wellbeing and correlate these predictions with observed neuroplastic changes. The results will provide insights into the potential therapeutic mechanisms of psychedelics and their impact on the interplay between language and subjective experience. This section will provide evidence for Hypotheses 3 and 4, showing that neuroplastic changes induced by DMT correlate with changes in wellbeing as predicted by the language-based model.
- **Chapter 5**: Discussion. This will serve as a main discussion, bringing together the findings from the previous chapters, setting out a future plan, and illustrating how the HOLISTIC theory can contextualise these findings.

Taken together, these three studies will contribute to a comprehensive understanding of the relationships between language, consciousness, and psychedelics. By testing the specific hypotheses outlined above, this thesis aims to advance our knowledge of how language-related brain processes mediate psychedelic experiences, predict well-being states, and are modulated by neuroplasticity. The findings will have implications for both theoretical models of consciousness and the development of novel therapeutic approaches involving psychedelics.

Chapter 2: The Neurobiology of Language Partially Mediates Alterations in Conscious Experience Induced by Psychedelic Drugs

Abstract

Psychedelic compounds profoundly affect conscious experience. This often involves “ego-dissolution” or diminishment of self and a sense of “oneness” or increased connectedness, correlated with changes in the DMN. However, the “self” is a largely language-mediated narrative construct. Language is also a cognitive tool for the categorisation of, e.g., perceptual information, whose absence might lead to less differentiated experiences. Thus, we hypothesised that the psychological effects resulting from psychedelics are at least partially due to the changes they induce in the neurobiology of language. We tested this hypothesis with meta-analyses, conducted separately for 39 “resting-state” and 32 task-based neuroimaging studies, comparing healthy participants administered “classic” psychedelics or ketamine to placebo controls. Both “resting-state” and task-based studies were primarily associated with significant increases in DMN and cerebellum activity. Additionally, at “rest”, psychedelics were associated with reductions in “early” auditory and surrounding language-related regions (e.g., the transverse temporal gyrus), with significant increases in “higher-level” language-related regions (e.g., anterior superior and IFG). During tasks, activity increased in both “early” and “higher-level” language-related regions. A hypothesis arising from these findings is that the profound impacts that psychedelics have on consciousness may partly be due to decreased access to lower-level acoustic categorical labels (words), with increases in associative semantic processing/flexibility, consistent with behavioural psychedelics research dating back to the 1950s. Results further suggest that the neurobiology of language might be a core mechanism in the efficacy associated with PAP and improved well-being following psychedelic use.

Introduction

“Psychedelic” compounds have been used for millennia for their ability to induce profound shifts in perception, emotion, cognition, and consciousness. They have potential therapeutic applications, ranging from mental health disorders to existential distress (Schimmel et al., 2022) and are undergoing active research as pharmacotherapies or combined with concurrent psychotherapy, called PAP (Schenberg, 2018). Indeed, psychedelic drugs are safe, not addictive, have few or no serious side effects, and may have transdiagnostic efficacy (Nutt et al., 2020; Schenberg, 2018). Supporting this, recent meta-analyses of well-controlled clinical trials demonstrate that PAP reduces addiction, anxiety, depression, and PTSD (Galvão-Coelho et al., 2021; Leger & Unterwald, 2022; Luoma et al., 2020; Romeo et al., 2020). More generally, psychedelics improve mental health and wellbeing in “neurotypical” populations (Aday et al., 2020; Swanson, 2018).

However, the underlying mechanisms by which psychedelics exert these effects remain largely elusive. There are multiple interrelated possibilities, representing different levels of neuroscientific analysis. These include “neuroplasticity” corresponding to the micro- and macroscopic level changes to the brain, the psychologically transformative effects that psychedelics have, e.g., the diminishment or loss of the self-construct and mystical experiences, or the interaction of neuroplasticity and environmental impacts (Swanson, 2018; van Elk & Yaden, 2022).

At the microscopic level, psychedelics impact both molecular (e.g., gene transcription) and (sub)cellular processes, including neuro-, dendrito-, and synaptogenesis (Banushi & Polito, 2023; de Vos et al., 2021); (Calder & Hasler, 2023; Olson, 2022). At a more macroscopic scale, psychedelics induce structural changes in both white and grey matter. DTI measures demonstrate an increase in white matter tract density (Aharon-Almagor & Barrett, 2022; Zeng et al., 2016); (Andrews-Hanna et al., 2014; Raichle, 2015); (Bouso et al., 2015); (Lepow et al., 2021; Mallaroni et al., 2023; Nichols et al., 2017; Ruban & Kołodziej, 2018). Finally, “resting-state” fMRI has revealed lasting changes to activity patterns at both the regional and network levels throughout the brain, with many studies highlighting changes to the DMN (Kwan et al., 2022); (Andrews-Hanna et al., 2014; Raichle, 2015).

Some of the changes to the brain caused by psychedelics may result from the psychological experiences they induce. These often start with sensory alterations, often visual (e.g., simple geometric patterns), creating a profound shift in perception (Winkelman, 2017). Moreover, psychedelics are known to elicit interoceptive and embodied effects, influencing how individuals perceive and experience their internal sensations and bodily awareness (Breeksema et al., 2020). These alterations in consciousness extend to cognitive functions such as flexibility and creativity, where psychedelics have been shown to modulate cognitive processes, potentially enhancing cognitive flexibility and creative thinking (Rifkin et al., 2020). Emotionally, psychedelics can evoke both positive and negative experiences, impacting emotional processing and regulation (Kaelen et al., 2015). Following this, a key experience induced by psychedelics at larger doses is “ego dissolution,” where individuals temporarily lose their sense of self and boundaries (Lebedev et al., 2015; Millière, 2017; Nour et al., 2016; Nour & Carhart-Harris, 2017; Orłowski et al., 2022; Tagliazucchi et al., 2016). This phenomenon is significant as it predicts subsequent changes in mental health and wellbeing (Kałużna et al., 2022; Mason et al., 2020). Finally, mystical experiences, characterised by a deep sense of interconnectedness, awe, and a transcendence of the self, are commonly reported (Nour et al., 2016). Given the overlap to “ego dissolution”, it is perhaps not surprising that such experiences are also predictive of long-term improvements in mental health and wellbeing (Kangaslampi, 2023; L. Roseman et al., 2018).

To understand the diverse experiential changes induced by psychedelics, several neurobiological models have been proposed, all sharing a common theme of reducing usual “mental constraints”. Historically, models have suggested that psychedelics act as a releasing mechanism on the brain's “cerebral reducing valve”, a concept implying that our brain usually limits the vast array of potential mental states to ensure effective functioning and survival (Swanson, 2018). This early concept seems to have influenced contemporary models. For example, , the “cortico-striato-thalamo-cortical” (CSTC) model proposes that psychedelics decrease the inhibitory control of the prefrontal and association cortices over the thalamus, lifting sensory filters (Vollenweider & Preller, 2020). Another, the Entropic Brain Theory (EBT), and its extension in the REBUS model, posits that psychedelics reduce the influence of the DMN, loosening the brain's top-down expectations while amplifying bottom-up sensory information (R. L. Carhart-Harris et al., 2014; R. L. Carhart-Harris & Friston, 2019). All models broadly concur that psychedelics diminish the usual regulatory mechanisms of the brain, largely accounting for the prominent changes in psychological experience.

These models are promising attempts to understand the neurobiological basis of psychedelic effects. However, in being whole brain models, mostly focused on very large-scale macroscopic structures, they lack specificity and detail, making it challenging to fully account for the complex mechanisms eliciting the diverse phenomenology of psychedelic experiences. Indeed, the PFC and DMN are composed of many cytoarchitectonic and functionally distinct subregions (Bzdok et al., 2013; Ongür & Price, 2000). More generally, the functions of those subregions are dynamically determined by which other brain regions those subregions are coactive or form networks with (Bullmore & Sporns, 2009). Over the last decades, tens of thousands of neuroimaging studies have elucidated the specific network arrangements underpinning affective, attentional, language, memory, and social functions (Andrews-Hanna et al., 2014; Power et al., 2011; Yeo et al., 2011). Understanding how these specific neurobiological systems are impacted by psychedelics could shed light on the variety of experiences they induce. This variability in neural systems and their responses to psychedelics is further compounded by individual differences in brain structure, connectivity, and baseline neurochemistry (Erritzoe et al., 2019; Preller et al., 2019). These individual variations in neural architecture and function may account for the diverse range of experiences caused by psychedelics, leading some researchers to characterise them as “super placebos” (Dupuis & Veissière, 2022; Hartogsohn, 2016). This term reflects how psychedelics can amplify the influence of individual neurobiological differences and contextual factors, resulting in highly variable and personalised experiences that go beyond the direct pharmacological effects of the substances.

We have previously proposed a “HOLISTIC” model of the neurobiology of language and its relationship to consciousness, mental health, and wellbeing that might serve to elucidate some specific aspects of psychedelic phenomenology (Skipper, 2022). In this model, the neurobiology of language is a whole brain process that connects words processed in “early” auditory regions to distributed regions of the brain involved in sensorimotor processing (e.g., auditory, visual, motor, somatosensory, and interoceptive regions) and memory (e.g., regions involved in autobiographical memory). Specifically, words flexibly organise our perceptual and more general experience of the world. This takes the form of categorically organising external auditory (e.g., auditory objects) and visual information (e.g., into colours, faces, and objects). Language also categorically organises internal information, like labelling lower-level interoceptive processing with emotional words, but also higher-level categories like our “narrative self”. The latter largely involves stories constructed and manipulated with words, allowing humans a range of extended cognitive abilities (e.g., planning future social interactions). These categorical processes are established with learning, e.g., labelling a colour as “pink” and can become positively or negatively entrenched, e.g., narratively referring to oneself as “stupid” in specific situations, or in certain mental health disorders.

From the perspective of this HOLISTIC model, transformative psychedelic experiences, like the feeling of “oneness” or loss of self, may be explained by the breakdown of the categorical functions of language. That is, the networks of the brain involved in language processing might cease to function typically and/or function at a reduced level or even potentially be temporarily suspended altogether. This transformation in the functioning of distributed language-related brain circuits would necessarily disrupt entrenched linguistic categories. Thus, increased "oneness" or connectedness can be seen as the result of the information processed throughout the brain being less differentiated due to a lack of categorical linguistic constraints. Similarly, "ego dissolution" or changes in self-perception would be linked to the change or diminishment in language functioning needed to maintain higher-level categories like the "narrative self". Supporting this proposal, a long history of research has consistently revealed that psychedelic compounds lead to a marked reduction in speech quantity and quality (Amarel & Cheek, 1965) and disrupt semantic processing, generally stated as an increased spread of semantic associations (Family et al., 2016; Spitzer et al., 1996). Furthermore, anecdotal descriptions of experience without language, e.g., like those of Helen Keller before acquiring language or that occur with aphasia, suggest atypical conscious percepts, arguably resembling aspects of the psychedelic experience (for a review, see [(Skipper, 2022)]. For example, individuals who had aphasia and who subsequently recovered, anecdotally report they experienced a heightened sense of connectedness and diminished sense of self [(Skipper, 2022)].

Further supporting this proposal are the specific neurotransmitter systems and brain regions impacted by psychedelic compounds. The 5-HT2A is a key target of psychedelics (Figure 1, red). This receptor is densely expressed on neurones in brain regions associated with the neurobiology of language (Figure 1, white outline)(Tagliazucchi, 2022). Indeed, a careful reading of the psychedelics neuroimaging literature demonstrates that many, if not the majority of studies, show that regions traditionally associated with language are impacted by psychedelics. These include regions are often associated with speech perception and language comprehension in the superior and middle temporal and IFG and regions more associated with speech production like the ventral aspects of pre- and primary motor cortices. Additionally, psychedelic effects are most consistently interpreted in relation to the DMN (Gattuso et al., 2023; Husain et al., 2022; Vollenweider & Smallridge, 2022). However, the DMN often works in concert with language-associated regions (as reviewed by Skipper, 2022). This helps make sense of the linkage of the DMN with the construct of the narrative self and its role in ego dissolution (under the assumption that the self is a largely language-mediated construct)(Bouso et al., 2015; Palhano-Fontes et al., 2015; Simony et al., 2016; Yeshurun et al., 2021).

To supplement this, since we also used a variety of ketamine studies, an additional analysis was conducted to investigate the overlap between NMDA receptor (NMDAR) distribution and the language-related brain regions mentioned apriori. Ketamine's primary mechanism of action involves NMDAR antagonism (Zanos and Gould 2018), leading to downstream effects on glutamate neurotransmission and synaptic plasticity (Zanos and Gould 2018; Autry et al. 2011). NMDA receptors are often located in the hippocampus, entorhinal cortex and basal ganglia. They are crucial for synaptic plasticity and neuronal communication.

A comprehensive analysis of NMDA receptor distribution using positron emission tomography (PET) imaging with the NMDA receptor antagonist [18F]GE-179 revealed high binding in the temporal cortex, including Wernicke's area, as well as in the IFG, encompassing Broca's area. This distribution pattern suggests a significant overlap between NMDA receptor density and key language-processing regions.This is what is shown in Figure 2. NMDAR density maps were obtained from Galovic et al. (2021).

The results indicate that NMDA receptor-rich areas exhibit significant overlap with key language-processing regions, such as the STG, IFG, and parts of the DMN. This finding suggests that ketamine's effects on language may be mediated through NMDA receptor modulation, consistent with psychedelics and 5HT2A receptors (Figure 1), contributing to the observed alterations in linguistic and cognitive processes during ketamine-induced ASCs.

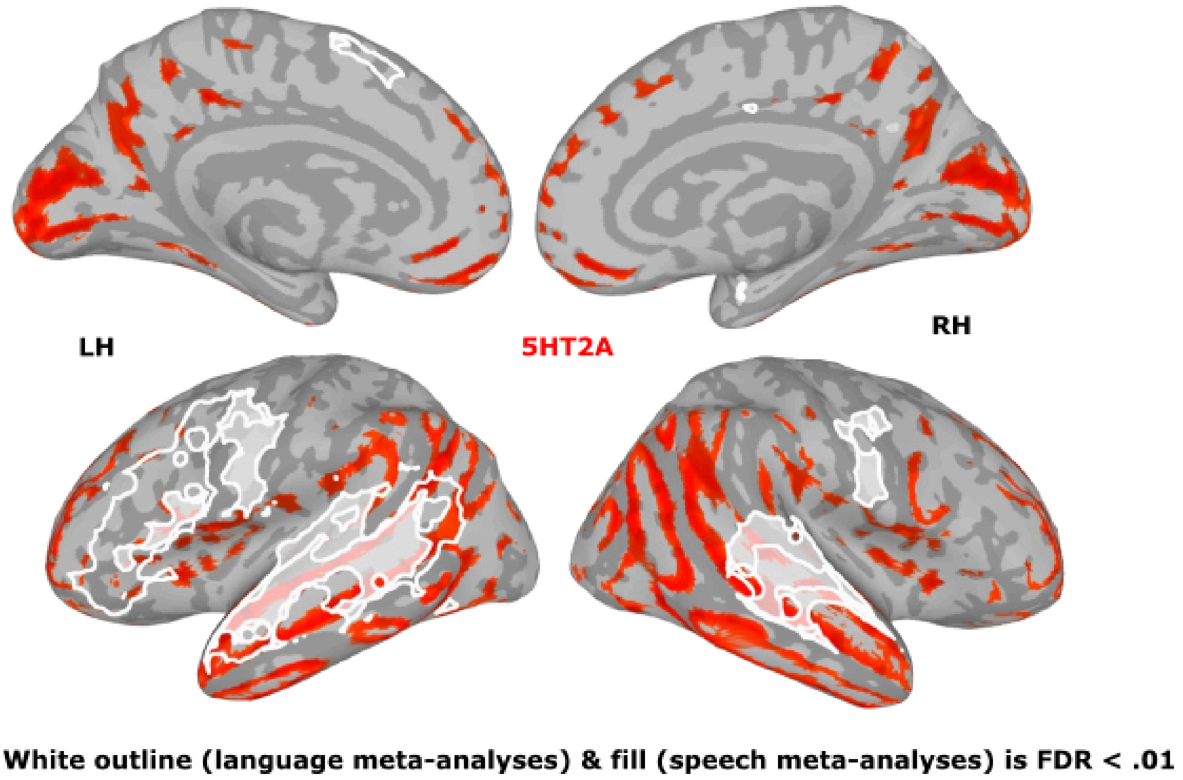


Figure 1. Brain map showing the overlap between language regions (white) and 5-HT2A receptors (red).

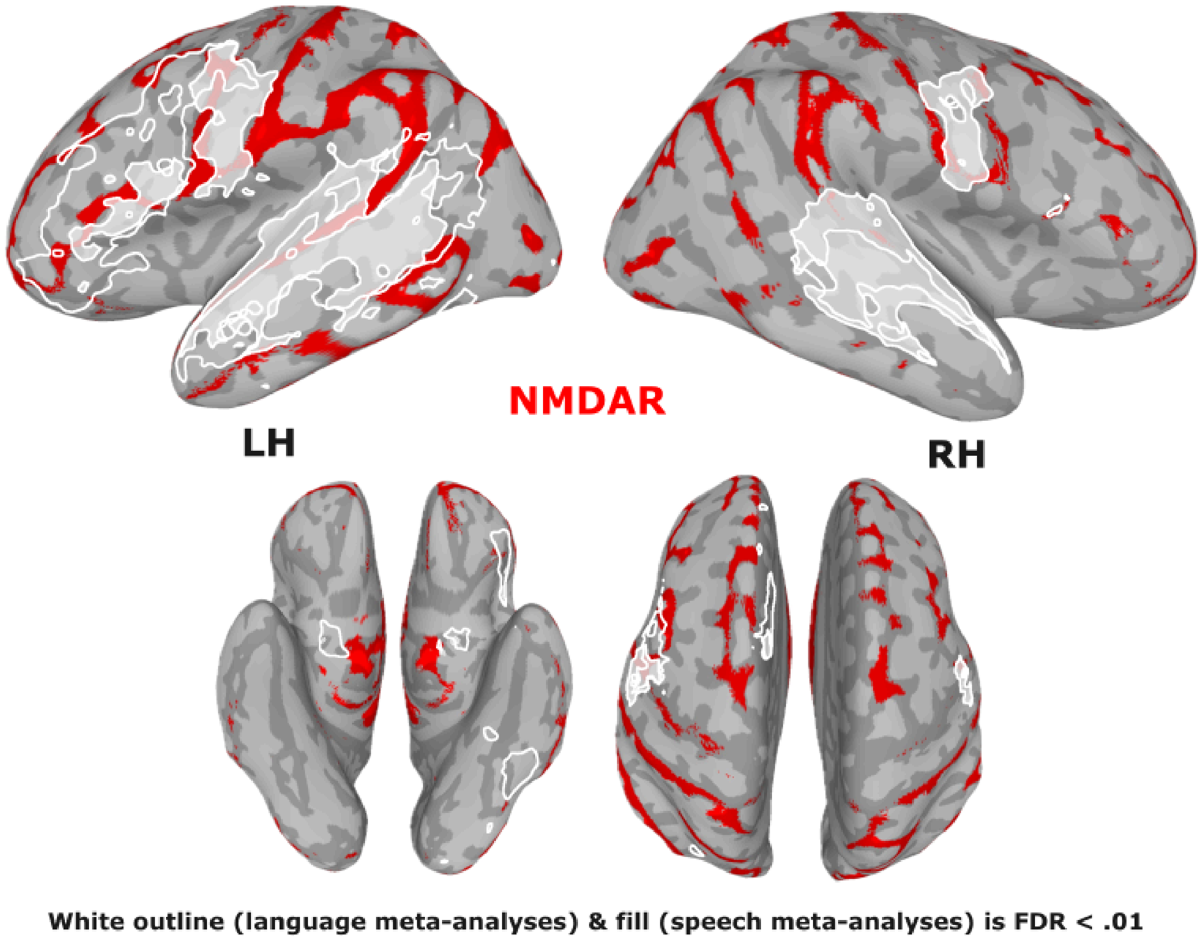


Figure 2. Brain map showing the overlap between language regions (white) and NMDAR (red), courtesy of Galovic et al. (2021).

Here we test the hypothesis that psychedelic drugs affect activity in language-related brain regions. Specifically, we expected reductions in engagement of “lower level” language regions (e.g auditory cortex, primary motor cortex) typically associated with speech given behavioural work suggesting reductions in language use during the psychedelic experience (reviewed above). We also anticipated changes in “higher level” regions typically associated with semantic processing like the anterior superior temporal (involved in semantic associations) and IFG and sulci (involved in semantic selection and/or retrieval) based on reported changes in semantic processing (though we did not have prediction about the direction of these effects). Finally, we examined activity differences in these regions during the “resting state” compared with task based studies. Though we expected differences, we had no specific hypotheses about how these might manifest.

To test these hypotheses, we used Seed-based d Mapping with Permutation of Subject Images (SDM-PSI) on a literature search of all neuroimaging studies of classic serotonergic psychedelics (e.g., DMT, LSD, and psilocybin), and the atypical psychedelic ketamine. We included ketamine primarily because, despite the limited number of neuroimaging studies on classical psychedelics, there is a larger body of research on ketamine. This is justified by the similarities in their subjective phenomenology and putative psychoplastogenic effects given that the subjective effects are comparable to serotonergic psychedelics (e.g., visual hallucinations and effects to the self and connectedness) as are some of the underlying neurophysiological effects (Johnston et al., 2023; Kadriu et al., 2021; Pallavicini et al., 2019). Following meta-analyses comparing the resting state and task-based conditions with placebo, we quantify the functional properties of resulting whole-brain and cluster-level activation patterns using pre-existing term-based neuroimaging meta-analysis (from Neurosynth). As there are several general neuroimaging meta-analyses of psychedelic drugs (Castelhano et al., 2021; dos Santos et al., 2016; Shepherd et al., 2023; Shinozuka et al., 2023; Soares et al., 2023), we conducted whole-brain analyses but focused on results associated with the neurobiology of language.

Methods

5HT2A and Language

The brains shown in Figure 1 were based on (Tagliazucchi, 2022), obtained from 95 healthy subjects using PET with [18F]altanserin as a radioligand. To conduct the neuroimaging ‘meta-meta-analysis’, we manually searched the BrainMap (Laird et al., 2005) and Neurosynth (Yarkoni et al., 2011) databases for terms related to language representations (e.g., “phonological”, “words”, “sentences”) and associated processes (e.g., “speech”, “semantics”, “syntax”). From the available terms, we conducted 28 BrainMap and 57 Neurosynth meta-analyses. Each of the resulting 85 meta-analyses was thresholded at $p < .01$ and corrected for multiple comparisons using false discovery rate (FDR) and a minimum cluster size of 50 voxels (400 ml). The results were combined into one neuroimage by count. Additionally, we conducted a one-sample “group” level statistical analysis with “software package” as a covariate (i.e., BrainMap or Neurosynth) and cluster-level thresholding to correct for multiple comparisons $\alpha = .01$, again using a minimum cluster size of 100 voxels (using ‘3dttest++’ available in the AFNI software package; for further information, see Aliko et al., 2023).

Likewise, the same meta-analyses and overall analysis was conducted on the NMDA receptors, with maps coming from Galovic et al. (2021).

Search

We conducted a search for neuroimaging studies of psychedelic and other drugs using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards (Figure 2)(Page et al., 2021). The purpose was to create a publicly available database to be used for a variety of neuroimaging meta-analyses, including for this article. The search used was:

((human or participant*) and (psychedelic* or hallucinogen* or entheogen* or psychotomimetic* or tryptamine* or LSD or "Lysergic acid diethylamide" or psilocybin or psilocin or "4-hydroxy-N, N-dimethyltryptamine" or ibogaine or DMT or "N,N-Dimethyltryptamine" or 5-MeO-DMT or "5-methoxy-N,N-dimethyltryptamine" or "2,5-Dimethoxy-4-iodoamphetamine" or "2,5-Dimethoxy-4-methylamphetamine" or "2,5-Dimethoxy-4-bromoamphetamine" or 2C-B or "2,5-dimethoxy-4-bromophenethylamine" or 2C-I or "2,5-dimethoxy-4-iodophenethylamine" or ayahuasca or mescaline or peyote or PCP or Phencyclidine or Salvia or ketamine or esketamine or ecstasy or MDMA or "3,4-Methylenedioxymethamphetamine") and (fMRI or MRI or "magnetic resonance imaging" or EEG or Electroencephalography or MEG or Magnetoencephalography or PET or "positron emission tomography" or NIRS or "near infrared spectroscopy" or neuroimag*))*

The asterisk is a wildcard that refers to truncation, meaning that all studies ending on the particular word were queried. We searched PubMed, Medline, PSYCinfo, and Web of Science. We also manually searched the reference lists of discovered papers.

The inclusion criteria for present purposes were that the papers had to have the following parameters: (i) healthy volunteers, (ii) neuroimaging resting state scans or active task-based, (iii) Talairach (TAL) or Montreal Neurological Institute (MNI) stereotaxic coordinate tables, (iv) use psychedelic drugs (e.g., ayahuasca, DMT, LSD, and psilocybin, see search above) or ketamine, and have a baseline and/or placebo control comparison.

Abstracts were screened and excluded if they were duplicate papers, retracted, irrelevant, not empirical (e.g., reviews), not involving human populations, non-classical psychedelics (i.e. MDMA), or ketamine with an anaesthetic dose. Full texts were then screened, resulting in 80 papers (published and completed before October 2022). A further nine were excluded due to not having acute scans. This resulted in 11 'resting state' and 11 active task based classic psychedelic studies and 28 resting state and 21 task based ketamine studies.

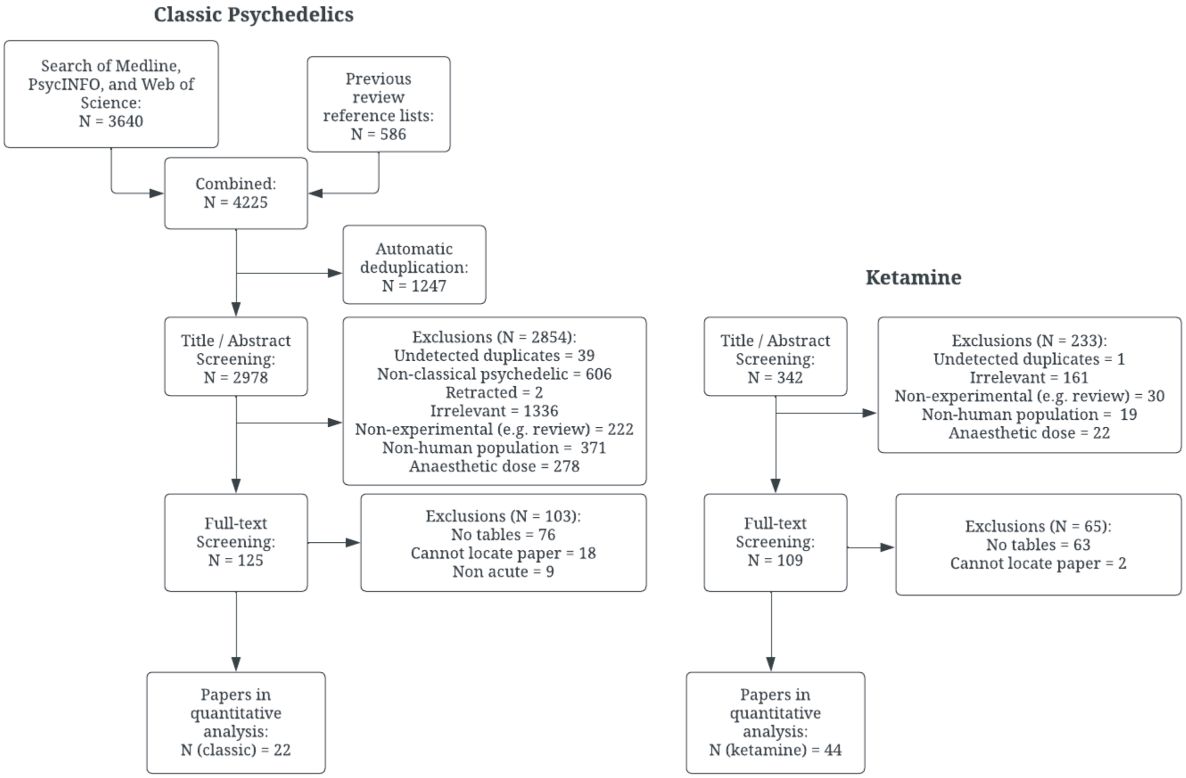


Figure 3. PRISMA flowchart of primary study selection. We searched for classical psychedelics (left) and ketamine (right) only and excluded studies that were duplicates, retracted, irrelevant, non-experimental (i.e., reviews), non-human population, at an anaesthetic dose of ketamine, and, finally, with no acute scans.

From these papers, the following data were extracted for our database: TAL or MNI coordinates; contrast name (i.e., whether drug > placebo or drug < placebo); t statistic (other statistics converted to t-values, see the next section); p-value; cluster size (i.e., the number of voxels); type of analysis (i.e., connectivity or voxel based); task or rest; label provided by author (i.e., the region they listed alongside the coordinates); table number and title (i.e., the table number reported in the paper alongside its title); authors name; year of publication; URL of the journal containing the paper; drug; dose; administration method; neuroimaging method; sample size; participants characteristics (age, gender, and condition, as in healthy or treatment resistant depression); study design (e.g., counterbalanced), and whether the study was structural or functional (we considered both). The key components of the studies are shown in Table 1 (below).

Meta-analyses

Seed-based d Mapping (SDM; v6.22; http://www.sdmproject.com/) was used to model psychedelic drug groups vs placebo controls. This method improves upon other meta-analytic software, including Activation Likelihood Estimation (ALE) and Multilevel Kernel Density Analysis (MKDA) in that it accounts for both increases and decreases of the measure, ensuring that activation or deactivation of a voxel is different from zero and ensures a less biased approximation of population effect size. Using multiple imputations, SDM also mitigates bias by considering a range of imputed values, providing results that are less prone to biases stemming from a single imputation method or set of imputed values, namely by taking into account positive, negative and non-significant results (Albajes-Eizagirre, Solanes, Fullana, et al., 2019).

We limited this analysis to studies collected from “classic” psychedelics or ketamine, during the resting state or completing an active task, with drug vs placebo, undergoing acute dosing, and in healthy volunteers, using dose (10 low, 11 medium, 1 high) as a covariate. The dose was determined through what was reported in papers, but adjusted for inconsistencies across categories. We chose to include dose as a covariate because it has been clearly shown that psychological effects follow a dose-respondent curve (Swanson, 2018).

We converted TAL coordinates into MNI coordinates and also converted all statistical scores into t-values as required in SDM. We then used the software, as previously described (Albajes-Eizagirre, Solanes, Vieta, et al., 2019). Some coordinates, however, were excluded due to incorrect reporting, i.e., within areas outside of the brain or with incorrect signs.

Briefly, the SDM-PSI software imputes the brain maps of statistical effects for the studies and carries out a standard random-effects meta-analysis in order to determine if the effects differ from zero, as conducted by Hedges and Olkin ((Hedges & Olkin, 2014; *[No Title]*, n.d.-a). First, SDM performs preprocessing, which generates lower and upper bounds of potential effect size images. For this, we used pre-defined/recommended settings, i.e., a gray matter template of sampling size 2 x 2 x 2 mm^3 voxels, with the number of imputations set to 50 and the number of permutations at 1000. We also used the default SDM kernel size (20mm) full width anisotropic Gaussian kernel at half maximum [FWHM]. Standard randomisation tests determined the statistical significance of the voxels (Radua et al., 2014).

Following this, we chose a mean analysis to calculate meta-analytic means, which incorporated Maximum-Likelihood Estimation (MLE) and MetaNSUE to estimate the most likely effect size and its standard error. The psychedelic vs placebo meta-analytic maps were created utilising a random-effects model, wherein each study was weighed by sample size, intra-dataset variability and between-dataset heterogeneity. Rubin's rules then combined the meta-analytic maps from different imputation sets to eliminate bias associated with single imputations by replacing missing or deficient values with two or more acceptable values, presenting a distribution of probabilities. SDM also uses a jackknife (or leave one out) procedure which ensures that a single study does not drive the results. This was compared to a null distribution for assessment of statistical significance (Rubin, 1988; Winkler et al., 2014).

Overlap Analysis

For the overlap between the resting state and task-based conditions, we used SDM's built-in linear regression model, which tests for differences and similarities between Z-map datasets, with each voxel in the datasets being independently considered. This is then weighted by the square root of the sample size and restricted to only predict possible SDM values of the variable, in this case resting state studies were coded as 1 and task-based studies coded as 0. Along with a regression slope, the resulting maps display areas of similarity and difference between the conditions (Radua et al., 2010; Radua & Mataix-Cols, 2009; Wise et al., 2016).

Correction

In all cases, Threshold-Free Cluster Enhancement (TFCE) was used to control the family-wise error (FWE) rate, with a significance level set at FWE $p < .01$ and a voxel extent threshold of ≥ 100 voxels. Unlike traditional thresholding methods that rely on setting an arbitrary voxel-wise threshold, TFCE enhances the sensitivity of statistical tests by taking into account the spatial structure of the data. It does this by enhancing the values of voxels based on both the magnitude of the statistical signal and the spatial continuity with surrounding voxels. Specifically, voxels that are part of larger, spatially extended clusters with higher values are given greater weight, reflecting the idea that such clusters are more likely to represent true, meaningful signals rather than noise. This enhancement process is performed across the entire brain, allowing for the identification of subtle, widespread patterns that might be missed by other methods (Smith & Nichols, 2009).

All coordinates are reported in the MNI space and which regions and networks they belong to using the Brainnetome Atlas (v1.0, https://atlas.brainnetome.org/)(Fan et al., 2016).

Reverse Inference

We used meta-analyses as a form of quantitative reverse inference to functionally characterise the results of the SDM analyses. That is, we then queried the open-source neurosynth.org database (version 0.7, released July, 2018), constructed from 507,891 voxel activation coordinates reported in 14,371 neuroimaging studies where terms appear at high frequency in the titles and abstracts (compared to studies where those terms do not appear) to determine which of more than a thousand terms were most associated with resulting clusters ($p < .01$ FDR corrected).

The platform automatically extracts activation coordinates from articles and associates them with cognitive terms based on the frequency of their appearance in the texts. All articles then undergo a full parse and are "tagged" with a set of terms that occur frequently within the article, generating an extensive list of terms. The Pearson correlation coefficients of the psychological words are then calculated between the term-based activation maps and our own maps (Gorgolewski et al., 2015; Poldrack, 2011; Yarkoni et al., 2011). Along with inputting whole brain maps, we also quantified the associations of significant individual clusters.

Whole Brain Spatial Correlations

We began by uploading our unthresholded beta maps to the Neurosynth Image Decoder (https://neurosynth.org/decode/). To ensure the robustness and relevance of our findings, we did not apply a threshold to the Z-map prior to querying NeuroSynth. This approach allowed us to capture the full spectrum of brain activity, thereby providing a more holistic understanding of the language-related processes represented in our data.

The NeuroSynth decoder compares the uploaded brain volumes with a large database of over 11,000 functional neuroimaging studies to produce a list of cognitive terms most associated with the input patterns. The decoder then utilises Pearson correlation to quantify the similarity between the input image and reference images in the database, which allows for a probabilistic inference of associated cognitive processes and a data-driven interpretation of brain function. For each of our beta maps, we extracted the top terms and their corresponding correlation values to identify the cognitive processes most likely associated with the observed brain activity. The whole brain map resulted in 1307 entries with corresponding Pearson scores, showing the strength of the association with our SDM map.

Individual Clusters

In addition to the whole-brain analysis, we also performed a more granular investigation by inputting specific coordinates into the Neurosynth platform. For this, individual coordinates corresponding to the peak of significant clusters from the initial analyses were entered manually into the Neurosynth database. This allowed us to retrieve related terms and processes associated with these clusters, offering deeper insights into the specific functions of the brain regions identified. The associated terms were then extracted based on their frequency and relevance, providing a detailed cognitive profile for each cluster.

We chose to focus on the top terms, but only those relating to cognitive and behavioural function and not anatomical, i.e., we disregarded terms like “central sulcus” and “precuneus.” The resulting terms represent the association of the brain regions reliably activated during the psychedelic experience compared to the control in neuroimaging studies of classic psychedelics and ketamine.

Comparator

To provide a comparative baseline and strengthen the claim of significant overlap between language and psychedelic-related brain regions, a meta-analysis of spatial navigation brain activity will be carried out. Spatial navigation, while also a complex cognitive function, utilises a distinct set of brain regions, allowing for a robust comparison.

Using NeuroQuery (https://neuroquery.org/) (Dockès et al. 2020), the areas of activation during spatial navigation tasks will be visualised based on the term ‘navigation,’ and then compared to the areas of activation found within the psychedelic meta-analysis.

Results

Search

The full search resulted in 4225 articles (assessed January, 2023). Of these 70 met inclusion criteria of neuroimaging participants engaged in acute resting state or active tasks under the influence of classic, serotonergic psychedelics or ketamine with a placebo control. These included 39 resting state and 31 task-based studies. Of those selected 6% (4) included ayahuasca, 1% (1) DMT, 14% (10) LSD, 10% (7) psilocybin and 69% (48) ketamine, with 15%

(11) of the classic psychedelic and 21% (15) of the ketamine papers being reanalyses of the same datasets, respectively.

Participants

Our study included, with classic psychedelics, 310 healthy participants (216 males and 94 females; mean age 29.0 ± 4.39 years), 72 of these psychedelic experienced, 7 not specified, with 250 being naive. While most studies adopted a within-subject, mixed repeated measures or crossover design, where the participants also served in a control group, i.e. taking a placebo as well as the experimental condition of consuming the psychedelic, some studies did have a separate control group. Overall, there were 29 unique controls (17 males and 12 females; mean age 26 years). For ketamine, the study included 783 healthy participants (382 males and 401 females; mean age 30.40 years), 206 participants were explicitly stated to be naive to ketamine, and the rest did not overtly specify. However, there were studies that included chronic ketamine users, which were disregarded from the overall analysis. The full demographics of the participants and vital information regarding the studies are shown in Table 1 and Table 2.

Table 1

Main characteristics across all 11 classic psychedelic and 27 ketamine resting state studies included in the meta-analysis.

	Study	Year	n	Age (mean years)	Females	Drug	Dose (mg/kg)	Dose level	Functional /Structural	Reanalysis
Classic Psychedelics	Alonso et al	2015	10		0	ayahuasca	0.75	High	Functional	No
	Bershad et al	2019	20	25	10	LSD	0.01	Low	Functional	No
	Carhartt-Harris et al	2016	12		4	LSD	0.075	Low	Functional	No
	Lewis et al	2017	29	24	10	psilocybin	0.16 – 0.215	Medium	Functional	No
	Madsen et al	2021	15	34	6	psilocybin	0.2 – 0.3	Medium	Functional	Yes
	Muller et al	2017	20		10	LSD	0.1	Low	Functional	No
	Muller et al	2018	20		10	LSD	0.1	Low	Functional	No
	Muthukumaraswamy et al	2013	15		0	psilocybin	0.02	Low	Functional	No
	Riba et al	2006	15		0	ayahuasca	0.01	Low	Functional	No

	Tagliazucchi et al	2014	15		2	psilocybin	0.02	Low	Functional	Carhart-Harris et al. (2012, 2013)
	Valle et al	2016	12		5	ayhuasca	0.75	High	Functional	No
Ketamine	Abdallah et al	2016	43	43	20	ketamine	0.5	High	Functional	Murrough et al (2015)
	Chen et al	2019	48	43.3	35	ketamine	0.2-0.5	High	Functional	No
	Downey et al	2016	40	27.1	33	ketamine	0.5	High	Functional	No
	Driesen et al	2013	30	29	10	ketamine	0.23-0.58	High	Functional	No
	Evans et al	2018	57	36	35	ketamine	0.5	High	Functional	Zarate et al (2006)
	Fleming et al	2019	53	31.58	22	ketamine	0.11	Low	Functional	Javitt et al (2018)
	Forsyth et al	2019	30	27.3	0	ketamine	0.25	Medium	Functional	No
	Gartner et al	2019	24	44.4	14	ketamine	0.25-0.5	High	Functional	No
	Herrera-Melendez et al	2021	33	47	18	ketamine	0.5	High	Structural	No
	Holfich et al	2015	30	25	12	ketamine	0.12	Low	Functional	No
	Holfich et al	2017	30	25	12	ketamine	0.12	Low	Structural	Holfich (2015)
	Holfich et al	2021	30	25	12	ketamine	0.12	Low	Structural	Holfich (2015)
	Hung et al	2020a	53	25.53	16	ketamine			Functional	Li (2017)
	Hung et al	2020b	56	25.2	19	ketamine			Functional	No
	Khalili-Mahani et al	2015	12		0	ketamine			Functional	No
	Kraguljac et al	2016	15	24.8	5	ketamine	0.25-0.27	Medium	Functional	No
	Li et al	2017	56	25.2	19	ketamine			Functional	No
	Li et al	2020	61	25	26	ketamine	0.5	High	Functional	No
	Mkrtchlan et al	2020	51	36	30	ketamine	0.5	High	Functional	
	Mueller et al	2018	17	27.42	0	ketamine	0.1	Low	Functional	Musso et al (2011)

Niesters et al	2012	12		0	ketamine			Functional	No
Nugent et al	2013	21	46	18	ketamine	0.5	High	Functional	Yes?
Rivas-Grajales et al	2020	35	42.2	16	ketamine	0.5	High	Functional	No
Spies et al	2019	30	25	12	ketamine	0.12	Low	Functional	Holfich (2015)
Woelfer et al	2020	53	24.4	21	ketamine	0.5	High	Functional	No
Wong et al	2016	13		0	ketamine	0.4	High	Functional	No
Zacharias et al	2019	24	27	0	ketamine	0.1	Low	Functional	Musso (2011)
Average		30	31.1	12					
Standard Deviation		16	8	10.5					

Note. Where there are blanks, the data was not available.

Table 2.

Main characteristics across all 11 classic psychedelic and 21 ketamine active task based studies included in the meta-analysis.

	Study	Year	n	Age (mean years)	Females	Drug	Dose (mg/kg)	Dose level	Functional/ Structural	Reanalysis
Classic Psychedelics	Barrett et al	2017	22	25.68	5	LSD	0.1	Medium	Functional	Prellet et al. (2017)
	Daumann et al	2010	14	32	6	DMT	0.15	Medium	Functional	No
	De araujo et al	2012	9	29	5	ayahuasca	0.1-0.2	Medium	Functional	No
	Duerler et al	2020	24	25.25	5	LSD	0.1	Medium	Functional	Preller et al. (2017)
	Duerler et al	2022	15	26.86	5	psilocybin	0.2	Medium	Functional	No
	Grimm et al	2018	25	24	6	psilocybin	0.16	Medium	Functional	Kraehenmann et al. (2014)
	Kaelen et al	2016	12	33	2	LSD	0.075	Low	Functional	No
	Kraehenmann et al	2015	25	24	9	psilocybin	0.16	Medium	Functional	No
	Preller et al	2017	22	25.68	5	LSD	0.1	Medium	Functional	No

	Preller et al	2018	22	25.68	5	LSD	0.1	Medium	Functional	Preller et al (2017)
	Schmidt et al	2016	18	31	9	LSD	0.1	Medium	Functional	No
Ketamine	Abel et al	2002	8	29	0	ketamine	0.23-0.5	Medium	Functional	No
	Abel et al	2003	8	28.75	8	ketamine	0.23-0.5	Medium	Functional	Abel et al (2002)
	Abel et al	2003	8	28.75	0	ketamine	0.23-0.5	Medium	Functional	Abel et al (2002)
	Breier et al	1997	17	30.4	2	ketamine	0.12-0.65	High	Functional	No
	Fu et al	2005	10	26.9	0	ketamine	0.65	High	Functional	No
	Honey et al	2004	12	31.17	6	ketamine	0.05	Low	Functional	No
	Honey et al	2008	15	29	7	ketamine	0.1-0.2	Low	Functional	No
	Lehmann et al	2021	53	24.37	29	ketamine	0.1	Low	Functional	No
	Liao et al	2010	85	26.8	26	ketamine			Structural	No
	Murrough et al	2015	38	38.1	17	ketamine	0.5	High	Functional	No
	Musso et al	2011	24	27	0	ketamine	0.1	Low	Functional	No
	Nagels et al	2011	15	27	0	ketamine	0.5	High	Functional	No
	Nagels et al	2017	15	27	0	ketamine	0.5	High	Multimodal	Nagels et al (2011)
	Northoff et al	2005	14	27	7	ketamine	0.6	High	Multimodal	No
	Reed et al	2018	59	36.1	37	ketamine	0.5	High	Functional	Evans et al (2018)
	Scheidegger et al	2016	23	25.5	11	ketamine	0.25	Medium	Functional	No
	Steffens et al	2016	27	25.57	0	ketamine	0.1	Low	Functional	No
	Steffens et al	2018	27	25.57	0	ketamine	0.1	Low	Functional	Steffens et al (2016)
	Sterpenich et al	2019	10	51	6	ketamine	0.5	High	Functional	No
	Stippl et al	2021	47	47.15	24	ketamine	0.25-0.5	High	Multimodal	No

Stone et al	2011	8	28	0	ketamine	0.65	High	Functional	No
Average		23	29.45	8					
Standard Deviation		17	6.12	9					

Note. Where there are blanks, the data was not available.

Meta-Analyses

Resting-State

After TFCE correction for multiple comparisons, and a cluster size threshold set to 20 voxels, a contrast of resting-state studies involving classic psychedelics with ketamine did not result in any surviving voxels. This justified combining all studies into one meta-analysis. After doing so, results show that these compounds produced significantly greater activity in a large distributed set of brain regions compared to placebo (Figure 3; Table 3).

In order of size, the clusters from this analysis peaked in the left cerebellum, right inferior parietal cortex, and left and right anterior medial cortices (Table 3, left column). While the largest clusters identified here are not traditionally considered language regions within classical frameworks, they exhibit substantial overlap with regions involved in various language functions (Table 3, right column). For instance, these were primarily associated with higher-level language (e.g., “word”, “sentence”, and “semanti”’) and memory-related linguistic processes (e.g., “semantic memory” and “verbal working”).

The fourth largest cluster peaked in the left IFG, overlapping with the language meta-analysis. This cluster included subregions like the pars orbitalis, triangularis, and opercularis (variously referred to as “Broca’s area” in the neuroimaging literature). Both the peak and all subregions were explicitly associated with language-related terms from “lower” (e.g., “phonologica”’) to “mid” (e.g., “lexical” and “words”) to “higher level” terms (e.g., “semantic” and “syntactic”; Table 3, left and right column).

Finally, other subregions overlapped with the language/speech meta-analysis (i.e., another cluster in the pars triangularis) and almost all of the resulting clusters contained subregions that were secondarily associated with language-related terms. These were most frequently “higher level” language-related terms like “semantic” and “syntactic” but included others (Figure 3, word cloud; Table 3, right column).

Table 3

Significantly greater activity for resting state classical psychedelic and ketamine neuroimaging studies compared to placebo controls.

Results					**Language-related Results**							
Regions	SDM-Z	P	Voxels	Terms	Regions	x	y	z	SDM-Z	P	Voxels	Terms
Left cerebellum, hemispheric lobule IX	4.892	0.001	3997	motor network, action observation, consolidation, real world, affective	Left fusiform gyrus, BA 37	-26	-40	-20	4.083	0.000999987	132	semantic, semantic memory, words
					Left cerebellum, hemispheric lobule VI, BA 19	-32	-62	-28	3.21	0.000999987	107	verbal working, rehearsal
Right inferior parietal (excluding supramarginal and angular) gyri, BA 40	5.721	0.001	3253	force, default network, motor	Right middle occipital gyrus, BA 19	56	-68	26	3.771	0.000999987	12	thinking, person, sentence
Right anterior cingulate / paracingulate gyri, BA 32	5.387	0.001	3511	preferences	Left superior frontal gyrus, medial, BA 32	-6	24	42	2.745	0.004999995	33	semantic, words, word, verbal, reading
Left inferior frontal gyrus, opercular part, BA 44	5.511	0.001	3183	phonological, semantic, word, reading, words, language, linguistic, orthographic, lexical, demands		-44	10	24				
					Left precentral gyrus, BA 6	-52	6	16	4.638	0.000999987	153	phonological, pseudowords, articulatory, rehearsal, speech
					Left inferior frontal gyrus, opercular part, BA 48	-50	16	20	4.785	0.000999987	133	syntactic, sentences, language, semantic, phonological
					Left frontal aslant tract	-42	10	10	3.873	0.000999987	119	rehearsal, nouns, word, phonological
					Left inferior frontal gyrus, orbital part, BA 47	-40	26	-12	2.827	0.001999974	88	semantic, comprehension, words, language, phonological
					Left middle frontal gyrus, BA 44	-44	14	40	4.479	0.000999987	72	semantic, sentence, syntactic, linguistic
					Left inferior frontal gyrus, triangular part, BA 47	-48	20	0	4.793	0.000999987	51	semantic, language, sentences, syntactic, verb
					Left temporal pole, superior temporal gyrus, BA 38	-54	6	-12	3.342	0.003000021	43	listening, auditory, language, speech, syntactic
					Left precentral gyrus, BA 9	-44	8	44	4.088	0.000999987	12	language, linguistic, languages, semantic, syntactic
Right middle frontal gyrus, BA 8	4.587	0.001	2265	working memory, working, memory, memory wm, load, task, memory task, wm, calculation, tasks	Right superior frontal gyrus, dorsolateral, BA 8	26	18	46	4.235	0.000999987	260	nouns

Left superior frontal gyrus, dorsolateral, BA 10	4.956	0.001	935	people, aging, older adults, remember, social cognition, social		-26	60	10				
					Left inferior frontal gyrus, triangular part, BA 48	-42	26	22	2.975	0.004999995	18	word, semantic, words, phonological, language
Right precuneus, BA 7	4.312	0.002	209	preparatory, adolescents, response inhibition, reaching, task								

Note. There were no regions significantly more active for the placebo condition. Activity is presented as the regions of the peak voxels in resulting clusters (left columns) and specific subregions that overlap with large-scale term-based neuroimaging meta-analyses of 'speech' and 'language' (right columns). Specifically, 'Regions' are the labels from X atlas, SDM-Z is the Seed-based d Mapping Z score, with 'P' being the voxel probability threshold: p = 0.001. 'Voxels' refers to the number of voxels in each resulting cluster and peak height threshold: p = 0.001, 'X Y Z' to the Montreal Neurological Institute (MNI) coordinates for the peak voxel in those clusters, , and 'Terms,' indicate the term-based meta-analytic neuroimaging meta-analyses associated with those peak coordinates according to Neurosynth, along with the z score of the terms in relation to the regions. All results are corrected for multiple comparisons using a TFCE (threshold free cluster enhancement) thresholded at α >= .01 and an additional cluster extent threshold of >= 100 voxels.

Alongside decoding individual clusters, we queried the Neurosynth database with the entire unthresholded Z-map to find the language-related terms that related to the whole brain map. Our findings are presented in the word cloud in Figure 3, notably terms related to "verbs" and "verbal" scored highly across the resting-state condition.

Whole-Brain Analysis

The resting-state results did not reveal the hypothesised reduction in activation for the psychedelics/ketamine groups relative to placebo controls after TFCE correction for multiple comparisons (Figure 4, Table 3; though see the "Overlap" section in which results reach significance). However, an inspection of the unthresholded results shows a very large set of activation decreases for psychedelics/ketamine participants overlapping language/speech meta-analyses that might have survived a different thresholding procedure (see Figure 4, blue). To further characterise this pattern, this section presents exploratory analyses examining results thresholded at p <= .01 without correction for multiple comparisons and completely untrehsolded results (as in Figure 4). In both cases, Neurosynth term-based meta-analyses are used as a reverse inferential procedure to describe resulting activity patterns.

For uncorrected but still thresholded results, negative clusters emerged in the left superior longitudinal fasciculus III (SDM-Z = -2.908, *P* = 0.001816690, 40 voxels) and left arcuate network, posterior segment (SDM-Z = -2.700, *P* = 0.003471613, 17 voxels). These were associated with "auditory," "production," "speech," "rhythm," "sentences," "vocal," and "language" term-based meta-analyses. The entire negative unthresholded map revealed associations with term-based meta-analyses like "categorical," "verbal fluency," "aphasia," and "word pairs." The entire positive unthresholded Z-map yielded terms related to language processing such as “language,” “phonological,” “speech,” “linguistic,” and “word.”

These results suggest that even though no significant clusters emerged after correction in the primary analysis, important language-related networks may be implicated when applying less conservative thresholds. The full set of results for both analyses is provided in Table S1 and S2 in the Supplementary Material.

Black outline is TFCE < .01

White outline (language meta-analyses) & fill (speech meta-analyses) is FDR < .01

Figure 4. Surface maps showing thresholded (*p* = 0.01) corrected with TFCE (black) and uncorrected results of resting state studies (underneath), with white representing the language (outline) and speech (filled in outline) meta-analyses from Neurosynth. Below this is a flatmap of the cerebellum, top and bottom views, and two wordclouds showing the terms from Neurosynth with a positive association (right) and negative association (left) and language related terms are highlighted in red. The word sizes indicate the Pearson's correlation coefficient associated with the term, with bigger implying higher and smaller having lower values.

Task-Based

Like the resting state, as described above, the task-based classic psychedelic vs ketamine studies resulted in no clusters surviving a threshold of .01 with the cluster size set to a minimum of 20. These studies were thus combined for analysis. This analysis revealed significantly increased activity in several brain regions compared to placebo (Figure 4; Table 4).

The most prominent clusters identified in this meta-analysis were observed in the left superior frontal gyrus, the left STG, and the right AG (Table 4, left column). These regions are strongly implicated in various linguistic functions (Table 4, right column). Specifically, the left STG is involved in phonological processing and auditory language comprehension.

Another large cluster was located in the left IFG, an area commonly associated with language production and processing, including Broca's area (Table 4, left column). This cluster included subregions such as the pars opercularis and pars triangularis, which are well-known for their roles in syntactic processing, lexical retrieval, and phonological tasks. Notably, these subregions are associated with both lower-level linguistic functions (e.g., "phonological processing") and higher-level functions (e.g., "syntactic processing" and "semantic retrieval"; Table 4, right column).

Additionally, other clusters exhibited substantial overlap with regions identified in language meta-analyses. For example, another significant cluster was found in the left AG, a region involved in complex language functions such as semantic processing and reading comprehension. Most of the clusters identified were associated with higher-level language functions, such as "semantic processing" and "syntactic structure," but also included terms related to basic auditory processing and verbal working memory (Figure 4, word cloud; Table 4, right column).

Other subregions overlapping with the language-related analyses included the left transverse temporal gyrus (or Heschle’s gyrus), left IFG, left pre- and postcentral gyri and the right STG, extending to the temporal pole (Table 4). Again, these regions are associated with many terms in the meta-analysis of language, both “lower level” aspects (centred around Heschl's Gyrus and the central sulcus) of and “higher level” language “syntax” and “semantics” (more anterior superior temporal and anterior IFG; Table 4). In addition to these classically defined regions, it can be seen that many of the brain regions had some association with language as determined by correlation with term-based meta-analyses.

Table 4.

Significantly greater activity for task based classical psychedelic and ketamine neuroimaging studies compared to placebo controls.

Results					Language-related Results							
Regions	SDM-Z	P	Voxels	Terms	Regions	x	y	z	SDM-Z	P	Voxels	Terms
					Left superior frontal gyrus, medial, BA 8	-2	30	52	7.755	0.000999987	211	categorisation, semantic
					Left supplementary motor area, BA 6	-10	12	60	7.318	0.000999987	197	sentence, sentences, read, comprehension, reading
					Left supplementary motor area, BA 8	-4	22	54	8.141	0.000999987	153	semantic, chinese, language
					Left supplementary motor area	2	14	44	7.301	0.000999987	112	verbal, phonological
					Left supplementary motor area, BA 32	-2	14	44	7.103	0.000999987	110	word, phonological, verbal, visual word, english
					Left superior frontal gyrus, medial, BA 9	-4	48	40	6.542	0.000999987	93	thoughts, comprehension, social, language
Right anterior cingulate / paracingulate gyri, BA 32	8.243	~0	4851	abuse, gain, reward, behavior, losses, error, errors, control, discriminative, pain								

					Right superior frontal gyrus, medial, BA 8	4	22	44	8.08	0.000999987	62	word
	7.089	0.001	1894	temporal, unexpected, discriminative, speaker	Right insula, BA 48	38	-20	10	6.819	0.000999987	347	auditory, sound, speech, sounds
					Right superior temporal gyrus, BA 48	58	-4	2	5.3	0.001999974	69	speech, speech perception, listening, vocal, speech production
					Right superior temporal gyrus, BA 22	54	-20	-4	6.68	0.000999987	59	listening, speech, voice, speech perception, spoken
					Right inferior frontal gyrus, triangular part, BA 45	48	18	4	6.683	0.000999987	42	heard, speaker
					Right arcuate network, posterior segment	58	-38	-4	6.793	0.000999987	20	auditory visual, auditory, language
					Right inferior frontal gyrus, triangular part, BA 47	46	26	-2	5.218	0.001999974	20	social, visual word
Right middle temporal gyrus, BA 21					Right superior temporal gyrus	58	0	4	5.24	0.001999974	10	pitch, vocal, auditory
					Left lenticular nucleus, putamen, BA 48	-30	-8	0	7.45	0.000999987	146	speech production
					Left superior temporal gyrus, BA 48	-52	0	0	5.158	0.001999974	36	auditory, vocal, speech, production
Left striatum	7.513	0.001	1531	sensorimotor, movement, movements, execution, sensations, finger tapping, handed, parkinson disease, tapping, dominant	Left heschl gyrus, BA 48	-38	-18	10	5.293	0.001999974	10	auditory, tone, pitch
					Right fusiform gyrus, BA 37	42	-54	-22	6.336	0.000999987	117	categories, category, social, social interaction, voice
					Right cerebellum, hemispheric lobule VI, BA 19	42	-66	-22	5.721	0.000999987	94	language network, reading, word form, perception, phonological
Right cerebellum, crus I	6.995	0.001	1540	conditioning, classical, symbolic, verbs, neutral pictures								

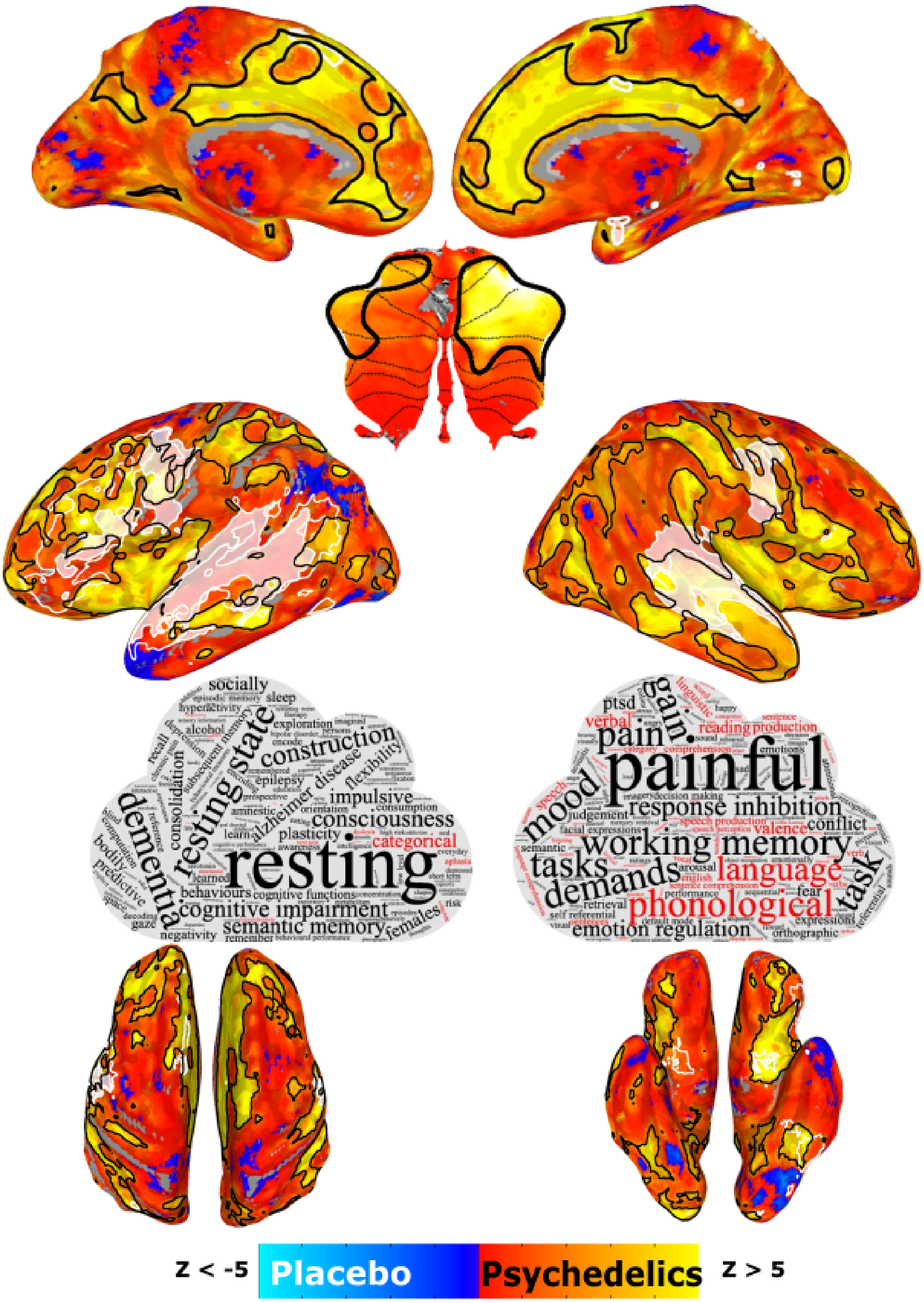
					Right cerebellum, crus II	28	-78	-40	5.634	0.000999987	87	thinking, mental states, mentalizing, words, semantic memory
					Right cerebellum, crus I, BA 19	28	-76	-26	6.276	0.000999987	67	mind, speech production
					Left inferior frontal gyrus, triangular part, BA 48	-40	24	28	4.93	0.003000021	107	semantic, word, reading
					Left inferior frontal gyrus, opercular part, BA 44	-56	16	20	5.91	0.000999987	80	sentences, language, syntactic, phonological, word
					Left precentral gyrus, BA 6	-58	0	38	5.268	0.001999974	74	production, speech, speech production
					Left middle frontal gyrus, BA 45	-40	40	18	6.349	0.000999987	52	rules, word
					Left inferior frontal gyrus, triangular part, BA 44	-54	18	26	6.164	0.000999987	45	sentence, semantic, phonological, word, language
					Left postcentral gyrus, BA 43	-60	-2	26	5.891	0.000999987	41	production, speech production, vocal, speech
					Left precentral gyrus, BA 44	-52	6	32	6.119	0.000999987	40	phonological, reading, rehearsal, letters, english
					Left inferior frontal gyrus, opercular part, BA 48	-48	14	18	6.806	0.000999987	39	language, word, syntactic, lexical, sentences
					Left precentral gyrus, BA 4	-58	0	30	6.085	0.000999987	22	rehearsal, production, repetition, repetition suppression, speech production
Left middle frontal gyrus, BA 9	7.774	0.001	1312	preparation	Left frontal inferior longitudinal fasciculus	-46	16	22	6.872	0.000999987	10	language, sentences, semantic, linguistic, comprehension

					Left superior parietal gyrus, BA 7	-24	-68	50	6.092	0.000999987	105	letter, reading
				finger, grasping, finger movements, finger tapping, tapping, sequential, movements, preparation, calculation, demands	Left inferior parietal (excluding supramarginal and angular) gyri, BA 7	-30	-58	48	5.395	0.001999974	54	word, reading, phonological, words, word form
Left postcentral gyrus, BA 2	6.914	0.001	680		Left angular gyrus, BA 7	-38	-70	42	5.68	0.000999987	24	semantic, lexical, words
					Right precentral gyrus, BA 6	56	-8	46	5.302	0.001999974	44	speech, lexical, vocal, auditory, spoken
Right supramarginal gyrus, BA 2	7.634	0.001	639	motor, tasks, finger, spatial, visual, execution, serial, movements, sequences, planning	Right precentral gyrus, BA 3	56	0	46	5.124	0.001999974	10	music, auditory, listening, speech, vocal
				chinese, reading, navigation, orthographic, faces	Right lingual gyrus, BA 18	20	-96	-10	5.747	0.000999987	73	reading, languages
					Right calcarine fissure / surrounding cortex, BA 18	22	-98	-4	5.619	0.000999987	66	reading, videos
					Right inferior network, inferior longitudinal fasciculus	22	-88	0	5.291	0.001999974	41	reading, chinese, english, bilinguals, speakers
Right inferior occipital gyrus, BA 18	6.116	0.001	303		Right calcarine fissure / surrounding cortex, BA 17	12	-98	-2	5.169	0.001999974	16	categories, lingual
Left middle frontal gyrus, orbital part, BA 47	6.495	0.001	202	reasoning, solving, rules, autobiographical								
Right middle occipital gyrus, BA 39	5.695	0.001	168	visual motion, navigation, mentalizing, contextual, motion, attention, encoding retrieval, retrieval, visual								
Left inferior temporal gyrus, BA 20	6.056	0.001	166	faces. face, visual word, words, selective, reading, language comprehension, pseudowords, recognition, expertise	Left inferior temporal gyrus, BA 37	-46	-44	-28	5.796	0.000999987	27	visual word, word form, verbs, word recognition, nouns

Right temporal pole, superior temporal gyrus	5.939	0.001	160	hypoactivation, taste	Right temporal pole, middle temporal gyrus, BA 38	46	14	-28	5.172	0.001999974	14	mental states, semantic memory, language, social cognitive
Left striatum	*5.916*	*0.001*	*111*	*reward, monetary, incentive, anticipation, incentive delay, gain ,monetary incentive, rewards, motivation, monetary reward*								

Note. There were no regions significantly more active for the placebo condition. Activity is presented as the regions of the peak voxels in resulting clusters (left columns) and specific subregions that overlap with large-scale term-based neuroimaging meta-analyses of 'speech' and 'language' (right columns). Specifically, 'Regions' are the labels from X atlas, SDM-Z is the Seed-based d Mapping Z score, with 'P' being the voxel probability threshold: p = 0.001. 'Voxels' refers to the number of voxels in each resulting cluster and peak height threshold: p = 0.001, 'X Y Z' to the Montreal Neurological Institute (MNI) coordinates for the peak voxel in those clusters, , and 'Terms,' indicate the term-based meta-analytic neuroimaging meta-analyses associated with those peak coordinates according to Neurosynth, along with the z score of the terms in relation to the regions. All results are corrected for multiple comparisons using a TFCE (threshold free cluster enhancement) thresholded at α >= .01 and an additional cluster extent threshold of >= 100 voxels.

Significant negative clusters in the task-based condition in classic psychedelics and ketamine compared to placebo when corrected for multiple comparisons with TFCE and thresholded at *p* = 0.01, were primarily in the left cerebellum, hemispheric lobule VI as well as the left fusiform gyrus, with some language-related terms like "audiovisual."



Black outline is TFCE < .01

White outline (language meta-analyses) & fill (speech meta-analyses) is FDR < .01

Figure 5. Surface maps showing thresholded (p = 0.01) corrected with TFCE (black) and uncorrected results of task based studies (underneath), with white representing the language (outline) and speech (filled in outline) meta-analyses from Neurosynth. Below this is a flatmap of the cerebellum, top and bottom views, and two wordclouds showing the terms from Neurosynth with a positive association (right) and negative association (left) and language related terms are highlighted in red. The word sizes indicate the Pearson's correlation coefficient associated with the term, with bigger implying higher and smaller having lower values.

Similar to resting-state, we produced a word cloud (Figure 4) of all language-related terms that were associated with the entire task-based Z-map. Results seem to suggest that more "reading" related terms are correlated with the task-based condition, i.e. "reading," "sentence comprehension," and "words."

Overlap/Contrast

In the overlap between resting state and task-based studies, these findings suggest an intriguing convergence of neural activity in regions associated with "early"/"low-level"' and "higher-level" language-related processes during both rest and task-based states under the influence of classic psychedelics and ketamine (Figure 5; Table 5).

Significant commonalities were observed in several brain regions. The largest clusters were found within the left precentral gyrus (Table 5, left column), which is heavily associated with language-related terms (Table 5, right column) like "phonological," "language," "verbal," and even specifically "chinese." This is also a region traditionally associated with Broca's area, a key region in language production. Another large cluster was located in the left superior longitudinal fasciculus III, with both the peak and sub region (left frontal aslant tract) being explicitly associated with language-related terms from "speech perception" and "speech production" to "tone", "pitch," and "letter" and "words." Further regions mainly consisted of "memory" and "autobiographical," terms, though these can be considered somewhat related to language.

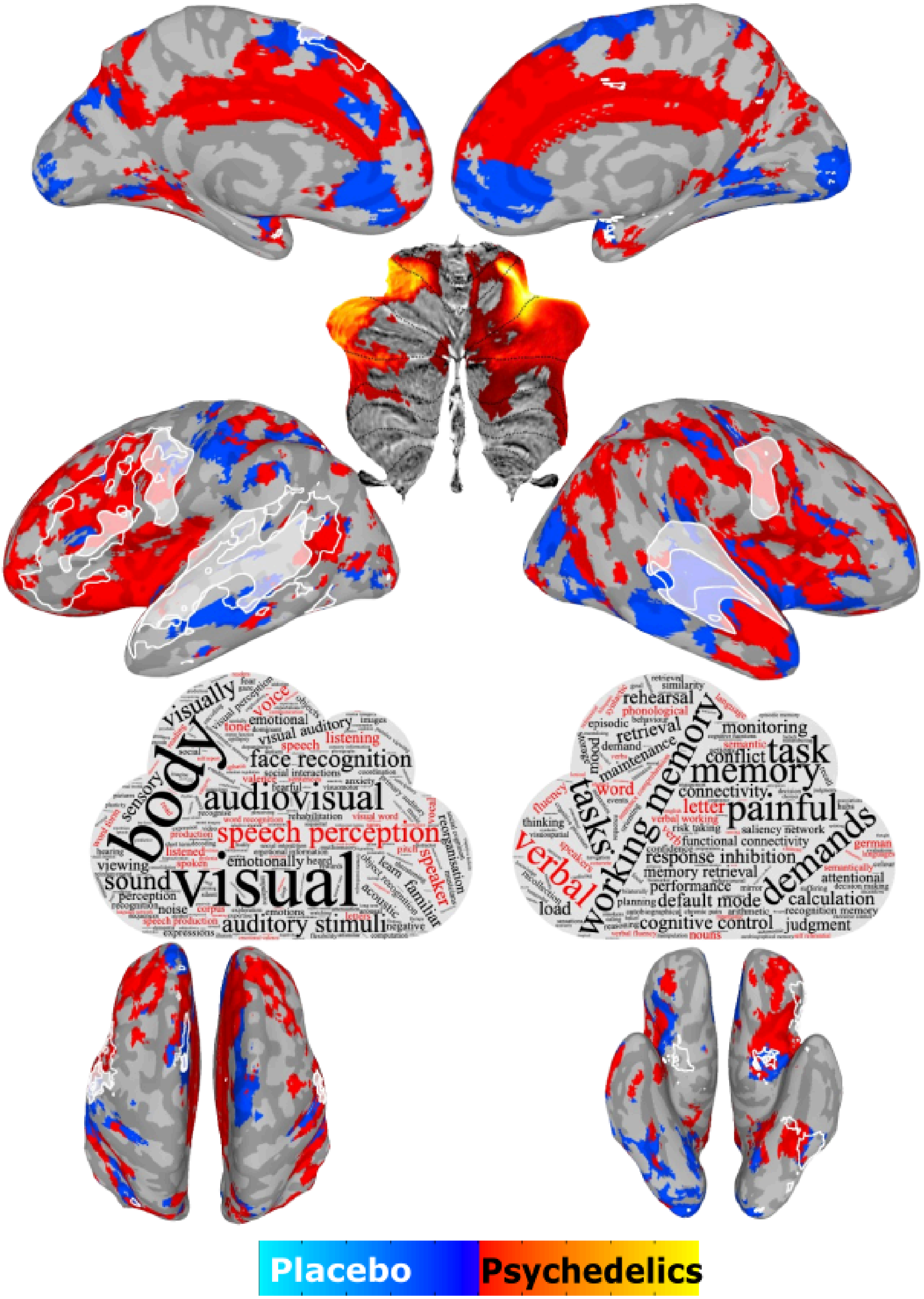
These findings underscore the complex network of brain regions involved in language and speech processing, with significant overlap observed in areas traditionally associated with both cognitive and motor aspects of language production and comprehension.

Table 5

Significantly greater activity for task based classical psychedelic and ketamine neuroimaging studies compared resting state studies.

Results					Language-related results							
Regions	SDM-Z	P	Voxels	Terms	Regions	x	y	z	SDM-Z	P	Voxels	Terms
Right median network, cingulum	2.729	0.003180385	1257	preparation								
Left precentral gyrus, BA 6	2.232	0.012822092	388	phonological, semantic, chinese, verbal, language, english, lexical	Left precentral gyrus, BA 6	-44	-2	40	2.232	0.012822092	163	phonological, semantic, chinese, verbal language, english, lexical
Left middle frontal gyrus, BA 10	2.279	0.011347413	223			-26	56	12				
Right supramarginal gyrus, BA 40	1.694	0.045157433	182	memory	Right angular gyrus, BA 39	50	-56	36	1.433	0.075950325	57	mentalising, default mode, default, autobiographica
Left superior longitudinal fasciculus III	2.249	0.012262821	147	heard, speech perception, speech, auditory, pitch, speech production, articulatory, production	Left frontal aslant tract	-54	4	16	1.781	0.037432253	37	production, phonological, psuedowords, rehearsal, articulatory, speech, pitch, letter, speech production, words, auditory language

Note. Activity is presented as the regions of the peak voxels in resulting clusters (left columns) and specific subregions that overlap with large-scale term-based neuroimaging meta-analyses of 'speech' and 'language' (right columns). Specifically, 'Regions' are the labels from X atlas, SDM-Z is the Seed-based d Mapping Z score, with 'P' being the voxel probability threshold: p = 0.001. 'Voxels' refers to the number of voxels in each resulting cluster and peak height threshold: p = 0.001, 'X Y Z' t the Montreal Neurological Institute (MNI) coordinates for the peak voxel in those clusters, , and 'Terms,' indicate the term-based meta-analytic neuroimaging meta-analyses associated with those peak coordinates according to Neurosynth, along with the score of the terms in relation to the regions. All results are corrected for multiple comparisons using a TFCE (threshold free cluster enhancement) thresholded at α >= .01 and an additional cluster extent threshold of >= 100 voxels.



White outline (language meta-analyses) & fill (speech meta-analyses) is FDR < .0

Figure 6. Surface maps showing thresholded (p = 0.01) corrected with TFCE results of task based combined with resting state studies, with white representing the language (outline) and speech (filled in outline) meta-analyses from Neurosynth. Below this is a flatmap of the cerebellum, top and bottom views, and two wordclouds showing the terms from Neurosynth with a positive association (right) and negative association (left) and language related terms are highlighted in red. The word sizes indicate the Pearson's correlation coefficient associated with the term, with bigger implying higher and smaller having lower values.

Discussion

Using neuroimaging meta-analyses, we tested the hypothesis that brain regions associated with both classic and contemporary views of the neurobiology of language play a central role in the effects of "classic" serotonergic psychedelic drugs and ketamine. Our results provide support for what has previously been suggested in the literature, i.e., that mostly medial regions associated with the putative "default mode network" are key regions impacted by these compounds. However, we also found evidence that some of the most impacted regions involved the inferior frontal and superior and MTG, among other regions typically associated with language processing. .

Specifically, we found no significant differences between classic psychedelics and ketamine, warranting combining compounds. For resting state studies, we found that the largest cluster of activity was in the left cerebellum compared to placebo controls or rest (Table 3; Figure 3). The third largest region of activity was the left posterior IFG. This large cluster extended into the anterior insula inferiorly and ventral premotor cortices posteriorly. Collectively, all of these regions are associated with articulation and speech production (Skipper et al., 2017; Skipper & Lametti, 2021). This was confirmed by meta-analytic associations (e.g., "articulatory" and "rehearsal"). That said, these and a number of other clusters were associated with other language functions (e.g,. "syntactic" and "semantic"). For task based studies, we found that the second largest cluster (after medial cortices) encompassed the IFG and superior and MTG (Table 4; Figure 4). Finally, the combined analysis showed increased activity for the psychedelics condition in left frontal and temporal regions like the IFG, STG, and MTG. Conversely, we observed decreased activity in RH homologues like the right IFG and right MTG. Taken together, these results indicate that the neurobiology of language may play an important role in the psychedelic state.

The Navigation System

To contextualise the observed overlap between language-related brain regions and those activated by psychedelics, it is pertinent to compare these findings with other cognitive processes, such as spatial navigation. Prior research has indicated that navigation relies on the MTL, including the hippocampus and entorhinal cortex, notably, the retrosplenial cortex is involved in translating between egocentric and allocentric spatial information, facilitating effective navigation, whereas language processing has been linked more prominently to the lateral temporal and prefrontal cortices (Burgess et al., 2002; Skipper et al., 2017). However, increasing evidence suggests that both systems engage distributed neural networks, making direct comparisons highly relevant.

By incorporating spatial navigation as a comparator, we assessed the specificity of the overlap between psychedelic-activated regions and language-related areas. Preliminary analysis indicates that while there is some convergence, particularly in regions like the PCC and the AG, since they are involved in memory and spatial information, respectively, the overall overlap between spatial navigation networks and psychedelic-activated regions is less pronounced than that observed with language-related areas. For instance, there is also a lot of activity under psychedelics in the IFG and DLPFC, as noted in the chapter, though these regions do not coincide with the navigation system.

This contrast is highlighted visually in Figures 7-9 (below), which show the activation patterns of the navigation system under both resting-state and task-based conditions with psychedelic influence. The dark outline in these figures represents the navigation system, while the red and blue activations indicate psychedelic-induced alterations. A more fine grained investigation could be conducted in future, like an FC or network analysis to elucidate conclusively whether language impacts the psychedelic experience as much as proposed in this thesis.

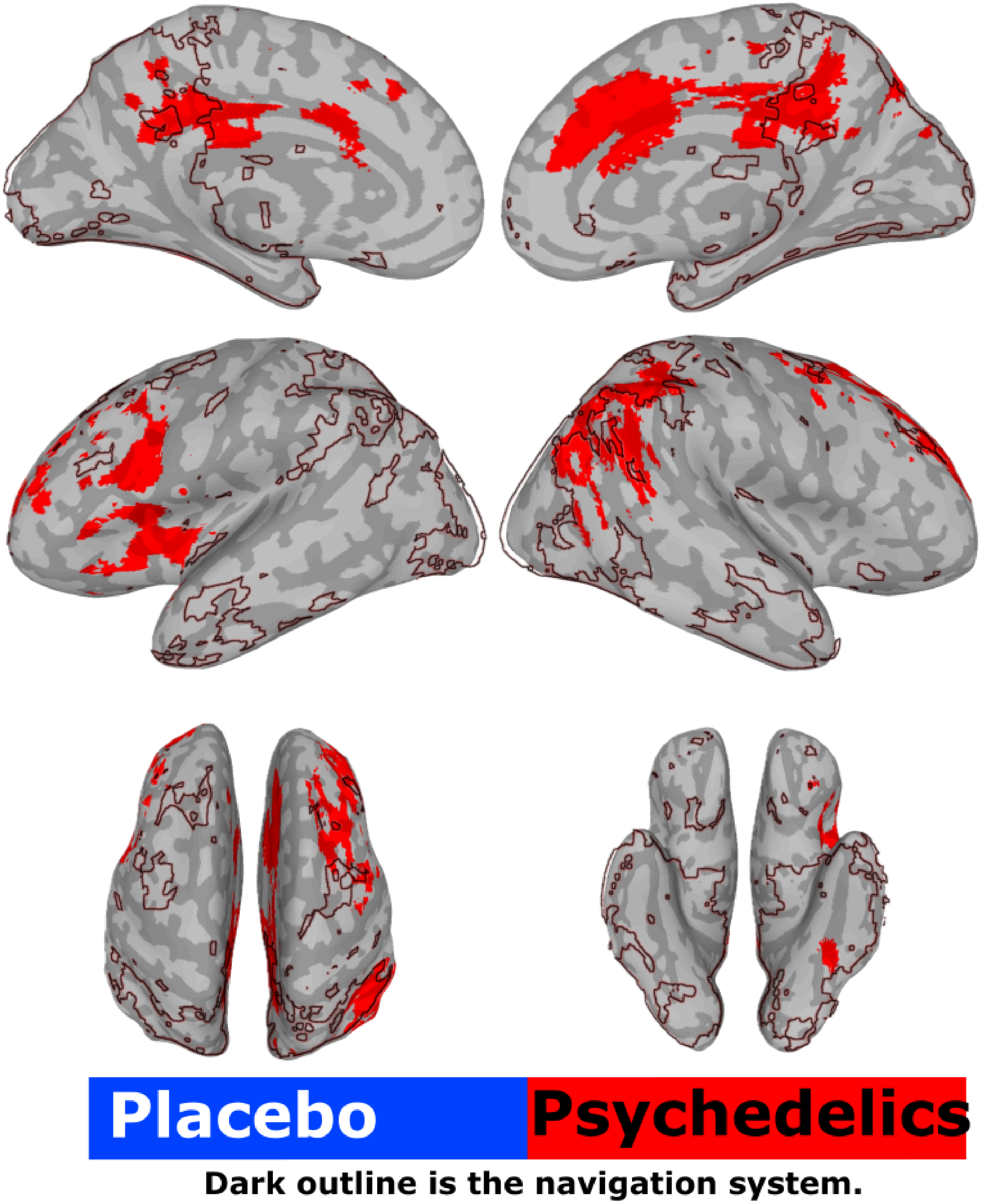


Figure 7. Surface maps showing thresholded (p = 0.01) corrected with TFCE results of resting state studies, with darker red outline representing the navigation system map from NeuroQuery.

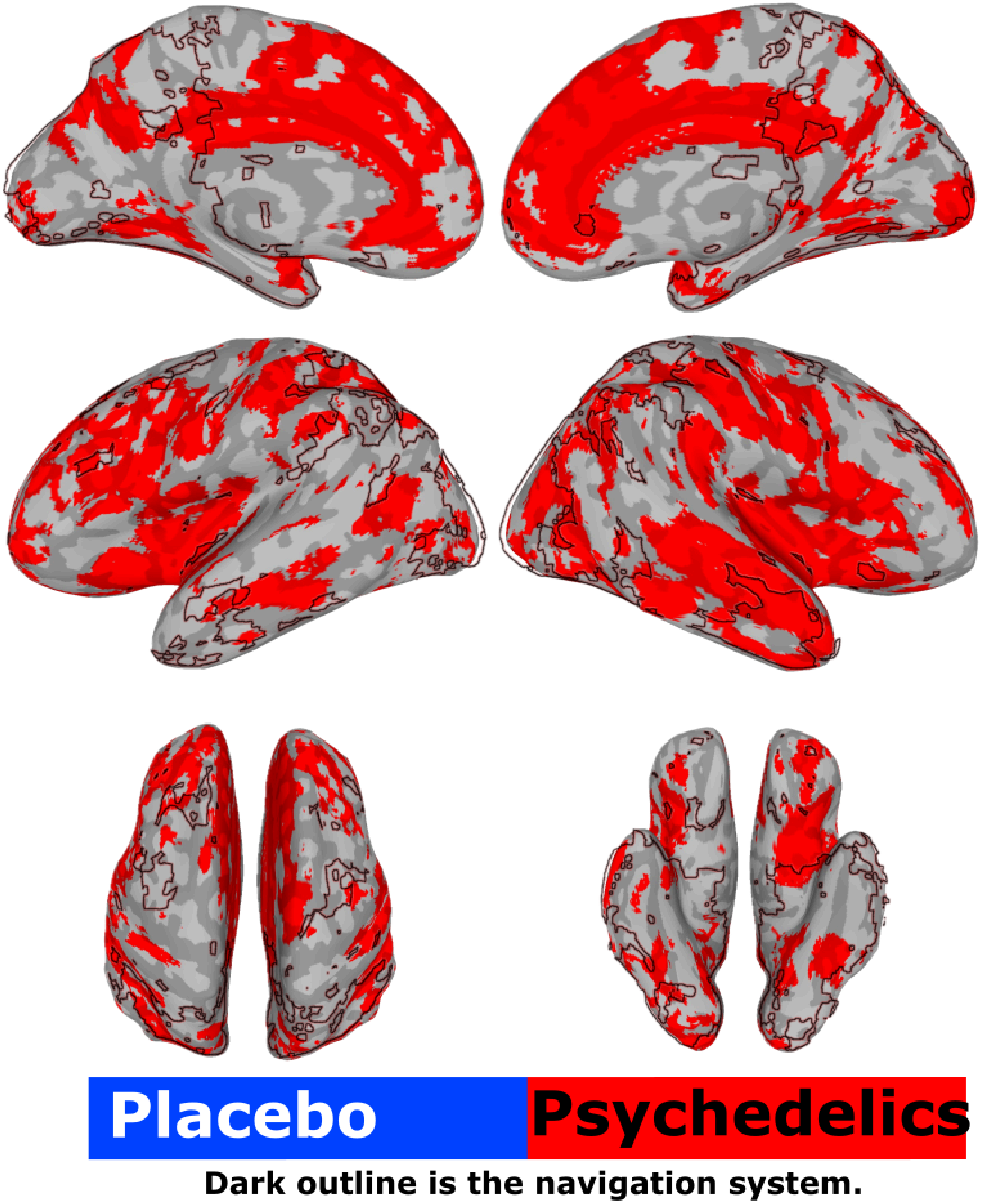


Figure 8. Surface maps showing thresholded (p = 0.01) corrected with TFCE (black) results of task based studies (underneath), with darker red outline representing the navigation system map from NeuroQuery.

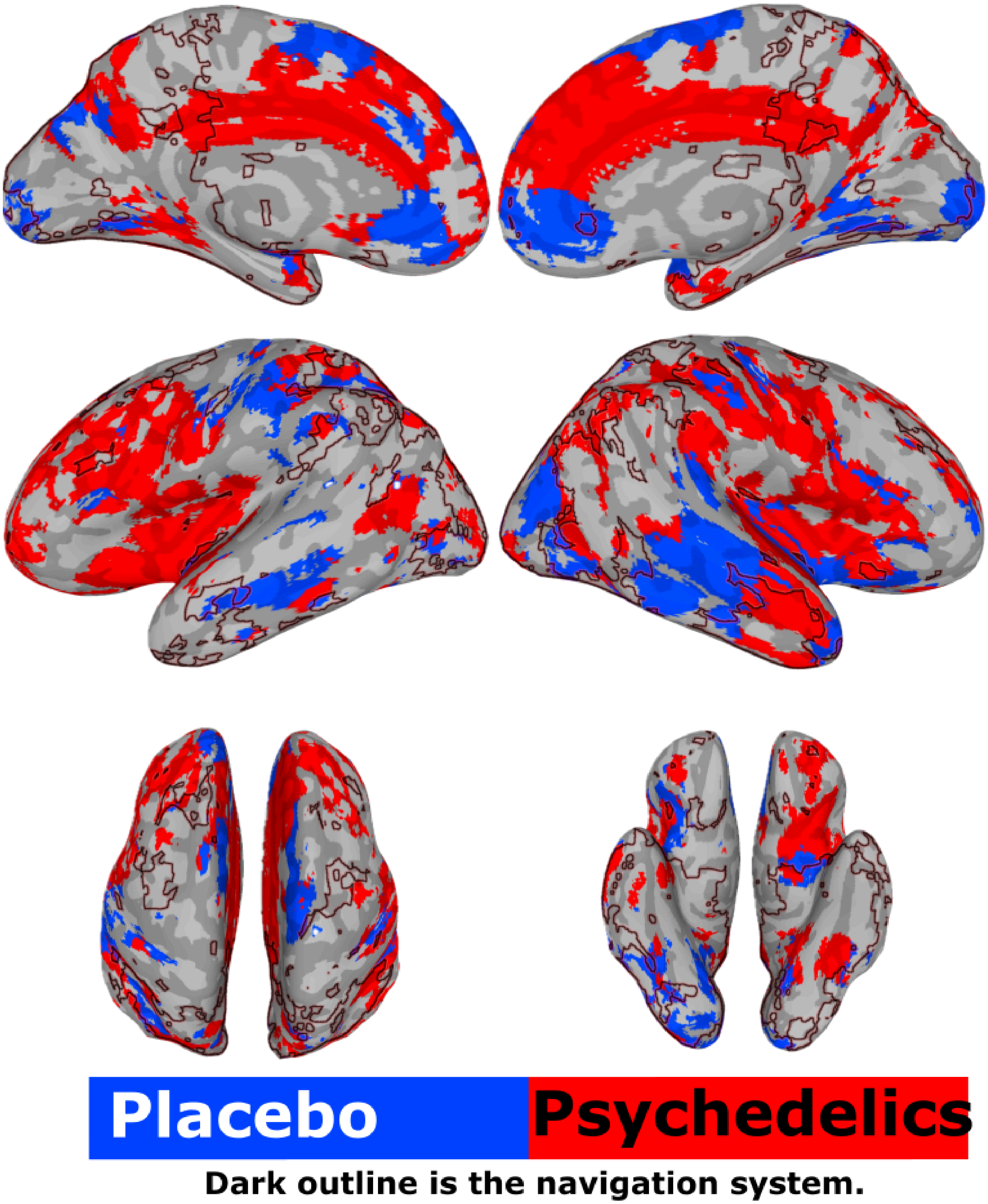


Figure 9. Surface maps showing thresholded (p = 0.01) corrected with TFCE results of task based combined with resting state studies, with darker red outline representing the navigation system map from NeuroQuery.

DMN

Most of the theory building around the neurobiology of psychedelic drugs centers around the DMN. For example, the REBUS and the anarchic brain theories, although whole-brain models, mainly suggest that psychedelics loosen high-level priors or beliefs, which, in turn, allows flow of bottom-up information and can lead to psychedelic phenomena such as ego dissolution. This theory follows the free-energy principle in that these high-level priors can be seen as counterparts to high-level intrinsic networks, such as the DMN (R. L. Carhart-Harris & Friston, 2019).

The DMN's involvement corroborates previous research, reinforcing its critical role in self-referential thought processes—a facet likely altered under psychedelics. The observed reduction in activity in key DMN regions, i.e. MPC, during resting state neuroimaging aligns with the established literature on psychedelics disrupting the typical functioning of the DMN. This decrease in DMN activity is in line with the subjective reports of ego dissolution and the blurring of self-other boundaries often associated with psychedelic experiences (Gattuso et al., 2023; Marguilho et al., 2023; Swanson, 2018).

Psychedelics & Language

Regarding the relationship between language and consciousness, the activation of brain regions associated with language, particularly those related to “lower level” aspects such as sound, speech perception, and speech production, our findings align with and contribute nuance to existing knowledge in this domain. Notably, our study revealed a general trend of reduced activity in early auditory, speech, and speech production regions during the psychedelic experience. This observation corresponds with the broader notion in the literature that psychedelics induce states characterised by reduced reliance on language and ineffable qualities (R. L. Carhart-Harris et al., 2012). The dampening effect on these early linguistic processing regions supports the idea that psychedelics may alter the typical neural underpinnings of language expression.

On the other hand, higher-level semantic processing regions might integrate these perceptions into coherent narratives or conscious thought. Our results also shed light on an intriguing aspect: an increase in activity in semantic regions such as the IFG, anterior STG, and MTG. This aligns with prior research suggesting that psychedelics enhance semantic processing and may promote a more flexible and associative form of thinking (Tagliazucchi et al., 2016). The heightened activation in these regions during the psychedelic experience implies an expansion or reorganisation of semantic networks, potentially also contributing to the novel thought patterns associated with psychedelic states (Kometer et al., 2015). At the same time, reductions in early linguistic regions implies a dynamic interplay, challenging the conventional view of language processing as a strictly hierarchical and localised function in the brain. The observed changes in neural activity during the psychedelic experience suggest a departure from the normative linguistic processing, inviting further exploration into the mechanisms underlying these alterations and their implications for consciousness and cognition.

This hierarchical processing, amplified under the influence of psychedelics, could lead to the enriched sensory experiences and ASCs reported by users. This connection underscores the role of language in shaping conscious experiences and highlights how psychedelic substances may modulate language-related brain regions to influence subjective experiences (Millière, 2017; Sanz et al., 2022).

The modulation of language processing regions could reflect alterations in self-awareness and subjective experience, highlighting the intertwined nature of language and consciousness. This involvement suggests that psychedelics may alter conscious experience through linguistic processes. Perhaps the disruption of normal language networks contributes to the altered sense of self often reported by psychedelic users (R. L. Carhart-Harris & Friston, 2019; van Elk & Yaden, 2022). By modulating activity in language regions, psychedelics could profoundly alter one's inner narrative and perception of reality.

Similarly, language-related regions are clearly affected in other studies, alongside the DMN, and specifically associated with ego-dissolution though no tables are provided in those papers to confirm this and discussion of language-related mechanisms is typically relegated to the sidelines (R. L. Carhart-Harris et al., 2013). Sometimes the very methods used preclude saying anything about language-related regions, e.g., the independent component analysis (ICA) based network parcellation in most if not all studies contain no network labelled “language” and only occasionally a network labelled “AUD” or a “sensorimotor” cortex network that includes auditory and surrounding regions (R. L. Carhart-Harris et al., 2012, 2013; Lebedev et al., 2015; Madsen et al., 2021; Tagliazucchi et al., 2016; Vollenweider & Preller, 2020). Furthermore, our results align with these emerging perspectives, suggesting that classic psychedelics may modulate the DMN in a manner that involves the recruitment and alteration of language-related regions during active tasks.

Furthermore, the involvement of language-related areas in the left SFG and left SMA during psychedelic experiences points towards a potential connection between language, psychedelics, and mental health/wellbeing. The activation of these regions, coupled with the reported mental health benefits and transformative states induced by psychedelic use, suggests that language processing may play a crucial role in the therapeutic effects of these substances on mental health (Payne et al., 2021; Raison et al., 2022).

Could targeting language areas enhance therapeutic outcomes? Anomalous language experiences are prevalent in psychosis (Crow, 1997), and dysregulated inner speech may contribute to mental health conditions like depression and anxiety (Alderson-Day & Fernyhough, 2015; Newby & Moulds, 2011). Thus, the relationship between language processing and psychedelics extends beyond consciousness, touching on mental health and wellbeing. The enhanced neural activity in language-related areas suggests that psychedelics could modulate the neural circuits that underpin key cognitive domains in mental health, such as ruminative inner speech, potentially highlighting a mechanism via which therapeutic benefits are achieved. This hypothesis could be directly tested in future trials by collecting metrics of language use and processing and relating this to neural activity and mental wellbeing pre-post psychedelics.

Moreover, the observed overlap between resting state and task-based neuroimaging findings in regions associated with reward processing and the DMN suggests that psychedelics could modulate self-referential thought processes, possibly attenuating the hyperactivity of the DMN linked with depressive symptoms. For instance, the ability of psychedelics to break down the ego-centric viewpoint, facilitated by changes in the DMN and language processing areas, can lead to reduced rumination, more positive self-appraisals and a reevaluation of personal narratives and beliefs.

This reevaluation process, coupled with enhanced semantic processing, might enable individuals to articulate and reframe distressing experiences or traumas, contributing to therapeutic outcomes in mental health conditions. Furthermore, the increased connectivity between sensory and semantic regions may enhance emotional and cognitive flexibility, allowing individuals to approach their experiences with newfound perspectives.

By normalising activity in language regions (Vollenweider & Kometer, 2010), psychedelics could potentially ameliorate such disturbances and foster greater self-awareness and psychological flexibility (R. L. Carhart-Harris & Goodwin, 2017; Watts et al., 2017). Such states may provide a conducive psychological environment for psychotherapeutic interventions (which, notably, are largely language-based), allowing individuals to explore and address underlying issues.

The potential of psychedelics to induce these neuroplastic changes emphasises the need for a holistic understanding of their impact on language processing and consciousness. By exploring these connections, we can unlock novel therapeutic pathways that integrate the neurobiology of language with psychedelic-assisted interventions, offering promising avenues for enhancing mental health and wellbeing. By elucidating the neural mechanisms through which language is modulated during psychedelic experiences, we can gain a deeper understanding of how these substances impact consciousness and potentially contribute to improved mental health and wellbeing.

HOLISTIC Model

Our HOLISTIC model proposes that psychedelics' effects on language processing may partly underlie their therapeutic potential (Skipper, 2022). In this model, language, with an emphasis on inner speech - is argued to be a fundamental mechanism for generating and maintaining ‘higher order’ consciousness, particularly self-awareness and meta-self-awareness. Specifically, there are six facets to the theory, titled loosely 1-6, which include “speech production” (“1.”), “language comprehension” (“2.”), “default mode” (“3.”), “semantic knowledge” (“4.”), “cognitive control” (“5.”), and “corticothalamic and thalamocortical” (“6.”), though, in reality, this is a much more simplified explanation as there are more than six components. Regardless, the components can be thought of as a loop, in which, firstly, a core set of inner speech production regions enable conscious “overhearing” of words. This then re-enters the loop to be processed by memory systems which mould the emotional, behavioural or linguistic output etc. Language-based thoughts from everyday cognitive processes are sent to memory systems in order to be recorded and associated, thus sustaining consciousness (Skipper, 2022). Integrating our findings into this framework, we discern a nuanced relationship between psychedelics, language, and consciousness, with implications for mental health and well-being.

From our findings, the involvement of language-related regions is clearly highlighted during classic psychedelic and ketamine experiences. This supports the HOLISTIC model's premise that higher-order language processing plays a crucial role in the altered states of consciousness induced by these substances. The activation of areas associated with semantic processing, verbal working memory, and word-related functions underscores the prominence of language in these states.

Additionally, the clusters in the left SFG and the left MFG, both associated with social cognition, mental states, and autobiographical memory, are indicative of self-reflective processes. These regions are critical for generating narratives and self-awareness, aligning with the model's premise. Also, the negative clusters in language-related areas in the resting state compared to the task-based condition may indicate a breakdown of language processes, contributing to ego dissolution. This challenges the conventional DMN hypothesis and suggests that the "I" consciousness is not solely associated with the DMN.

By this model, mental health and wellbeing are explained by entrenchment. Selected responses may become entrenched over time due to learning and use, which makes them more automatic, and, therefore less accessible to conscious awareness. Some of these entrenched responses may be negative, resulting in, for example, self-referential negative biases and decreases in mental health and wellbeing. Thus, targeting these entrenched connections is a goal of psychotherapy (Skipper, 2022).

Furthermore, we posit that the disruption of conventional language processing by psychedelics may serve as a catalyst for therapeutic and transformative experiences. The temporary removal of linguistic constraints allows for a more direct and holistic engagement with emotions, memories, and self-reflection. This shift in linguistic processing aligns with the reported therapeutic potential of psychedelics, offering a unique avenue for exploring novel approaches to mental health and wellbeing (Beswerchij & Sisti, 2022; Nichols, 2016).

Therapy can target multiple networks that include entrenched connections between inner speech cores, their connected peripheries, default mode regions, lateral prefrontal regions, and/or corticothalamic/thalamocortical connectivity used to select contextually “appropriate” responses. Indeed, neuroplasticity in some or all these network connections is likely the unwitting target of psychotherapy (Butler et al., 2006; Pittenger & Duman, 2008). Such neuroplasticity might be induced in more efficient manners. For example, “classical” or serotonergic psychedelics, like psilocybin, LSD, and DMT all induce neuroplasticity (Grieco et al., 2022). Neuroimaging results suggest that changes in the relationship between the default mode and other networks during acute intoxication are one target of psychedelic neuroplasticity

(Atasoy et al., 2017; Fox et al., 2018; Vollenweider & Preller, 2020). Thus, targeting inner speech core-periphery arrangements, the DMN, and prefrontal selection processes with psychotherapy following the administration of psychedelics might permit less rigid word, meaning, and contextual associations. Indeed, this might underpin the promising results of PAP (Mertens & Preller, 2021).

In summary, our study, viewed through the lens of the HOLISTIC model, suggests that psychedelics may induce a reconfiguration of language processing, facilitating a more integrated and immersive cognitive state. This alteration has implications for consciousness, expanding our understanding of how psychedelics may influence mental health and wellbeing through their impact on language and socio-emotional processing within a holistic framework.

While the initial premise of this chapter posits that language processing is distributed across a network of brain regions, the meta-analysis has, by necessity, focused on areas traditionally associated with language. This approach was taken to provide a clear and quantifiable analysis of overlap with psychedelic-induced brain activity. However, it is crucial to acknowledge that this focus does not negate the distributed nature of language. While certain regions are emphasised due to their prominence in the data, it is essential to consider them as integral components of a widespread, interactive network that collectively supports language processing. Future analyses will incorporate network-level analyses to better capture the interactions between these regions.

Limitations

One limitation of the current findings is the scarce amount of published literature on the topic. Indeed, many of the papers do not have tables in them and 18 are reanalyses of the same data. There is also a large heterogeneity of analysis approaches in the studies that we combined over because of limitations in sample size, so we included both connectivity and voxel-based studies. Since the smallest sample size is around 15, more data is needed to determine if these results are stable over a larger array of resting and task based studies, which also have a high degree of heterogeneity.

Due to this already small sample size, placebo-controlled conditions were also included in the work, though they present a methodological challenge in psychedelic research due to the inherent difficulty in maintaining functional blinding. For instance, participants receiving psychedelics often become aware of their treatment condition through distinctive perceptual and psychological experiences, a phenomenon known as functional unblinding. This issue is critical because expectancy effects can significantly influence subjective and neural responses, potentially confounding results.

In the current meta-analysis, efforts were made to mitigate this issue by including studies that explicitly assessed and reported on blinding integrity and by comparing neuroimaging findings against rigorous placebo conditions. However, it remains possible that residual expectancy effects influenced the neural signatures observed. Future research should continue exploring innovative placebo methodologies, such as active placebos that produce mild psychoactive effects, which is the overall plan for the UNITy study (discussed in Chapter 4), to better isolate the pharmacological effects of psychedelics.

Likewise, with regard to interpretation, we have no direct evidence for the knocking out of or increased involvement of language regions except the (quantitative) reverse inference procedures. There are in fact no neuroimaging studies that we are aware of in which anything language-related is explicitly manipulated.

Another critical aspect of this debate is whether semantic and conceptual processing should be categorised strictly as linguistic. While some scholars argue that semantic cognition is inseparable from language, others contend that conceptual representations are amodal and shared across cognitive domains (Binder & Desai, 2011). This distinction is crucial for interpreting the results of studies investigating consciousness through linguistic frameworks. If semantic networks extend beyond language-specific processing to encompass general conceptual structures, then it may be more appropriate to frame these findings in terms of shared cognitive representations rather than a purely linguistic mechanism.

To address these concerns, a more precise operationalisation of the language network is necessary. Future research should delineate the extent to which language-specific regions interact with broader conceptual processing hubs and clarify whether observed effects on consciousness arise from linguistic functions per se or from more generalised cognitive representations. Incorporating neuroimaging and lesion studies could further refine our understanding by identifying the functional boundaries of the language network and its role in structuring conscious experience.

Implications

Despite the limitations, overall, the present study contributes to our understanding of the effects of classic psychedelics and ketamine on language and memory systems, highlighting the need to reconsider the traditional DMN theory and adopt a more nuanced framework to capture the complex interplay between psychedelics and language processing.

Thus, the aim of this report is to widen the field of research and add credence to the theory that language is not just a stimuli, but a tenet in sustaining higher order consciousness, with the hopes that language will become more ingrained in clinical science.

There are many unanswered questions in the field due to, as previously mentioned, language not being recognised or detailed in reports. So one further piece of research could be to account for variables in language across cultures, social status, gender, etc, and consequently their reports on drug-induced experiences. We hope the current findings serve as a "first step" for more controlled work that is better able to assess the mediating role of language processes on cognitive and mental health outcomes following psychedelics. Understanding the neurobiological foundations of language-mediated alterations in conscious experience induced by psychedelics has far-reaching implications, extending beyond the realms of neuroscience. This knowledge can inform therapeutic interventions, enhance our understanding of consciousness itself, and potentially reshape our conceptualisation of language and its role in shaping our subjective reality.

Conclusion

In conclusion, our analysis replicates previous findings concerning the medial brain regions, such as the cingulate, while introducing the cerebellum as a novel and intriguing player in the psychedelic narrative. In addition, the intricate relationship between language-related regions and psychedelic effects emerges from our analysis, underscoring the potential for psychedelics to alter conscious experience through linguistic pathways. Furthermore, we propose a novel connection between language processing regions affected by psychedelics and their broader implications for mental health and wellbeing. This connection could form the basis of a holistic model linking language processing with mental wellness, mediated through psychedelic experiences.

In conclusion, our study's findings, in conjunction with the HOLISTIC theory, highlight the pivotal role of language and social interaction in shaping the narrative self and personal identity. Classic psychedelics and ketamine both exhibited clear effects on language-related brain regions, suggesting the potential for alterations in narrative processing, self-expression, and self-reflection. These insights have implications for therapeutic applications, as these substances may offer unique opportunities for individuals to explore and reconstruct their personal narratives, leading to transformative experiences and improved psychological wellbeing.

Chapter 3: Language-based Predictive Modelling of Wellbeing using fMRI

Introduction

The World Health Organisation (WHO) defines mental health as "a state of wellbeing in which an individual realises his or her own abilities, can cope with the normal stresses of life, can work productively and is able to make a contribution to his or her community". But what occurs when this goes awry? Mental health disorders pose a significant global socioeconomic and healthcare burden, with an estimated 450 million people affected worldwide (Organization and Others 2014; World Health Organization 2018). The high prevalence and substantial impact of mental health disorders underscore the need for innovative approaches to understanding, predicting, and promoting mental wellbeing.

In recent years, the intersection of neuroscience and language processing has emerged as a promising avenue for investigating mental health (Tausczik & Pennebaker, 2010). Language, as a fundamental aspect of human cognition and communication, provides a window into an individual's thoughts, emotions, and overall mental state (Pennebaker et al., 2003). The words we use reflect our inner experiences, and the way we process and respond to language can influence our cognitive and emotional well-being (Saxbe et al., 2013).

In particular, the words we choose can significantly impact our mental health, reflecting our internal states and affecting how we process and respond to the world around us. Indeed, psychological ‘talking’ therapies, definitionally, are delivered via the medium of language and allow individuals to reappraise their cognitions and develop new metacognitive skills - illustrating the central role language can play in supporting (or undermining) mental health. Various studies have highlighted how specific word types—such as cognitive terms, concrete nouns, and pronouns—can illuminate aspects of our mental health. For instance, cognitive terms like "think" and "reason" are associated with higher cognitive processing and resilience, indicating robust mental health (Tausczik & Pennebaker, 2010). Cognitive process words can also indicate more nuanced thinking and better psychological adjustment (Pennebaker et al., 2003; Ramírez-Esparza et al., 2017). Concrete nouns have been found to reduce rumination and promote mindfulness (Watkins & Moulds, 2005). Conversely, the use of first-person pronouns like "I" and "me" can reflect self-focus, which may oscillate between healthy self-reflection and detrimental rumination (Carey et al., 2015; Zimmermann, 2018). Yet, the broader implications of these findings across diverse linguistic contexts and their neural underpinnings remain underexplored.

Numerous studies have explored the link between subsets of these word categories and mental health outcomes, revealing that specific linguistic patterns are associated with psychological distress, depression, and anxiety (Rude et al., 2004; Zimmermann, 2018). For instance, as mentioned, individuals with depression tend to use more first-person singular pronouns, negative emotion words, and fewer positive emotion words compared to healthy controls (Pennebaker & Lay, 2002; Rude et al., 2004). Similarly, the use of causal and insightful language has been linked to improved mental health and wellbeing (Pennebaker et al., 1997)

Existing research on language and mental health has primarily focused on a limited set of linguistic features, such as pronouns, emotion words, and cognitive words (Tausczik & Pennebaker, 2010). However, language is a rich and multifaceted construct, encompassing a wide range of word categories that may contribute to mental wellbeing in unique ways. To gain a more comprehensive understanding of the language-brain-well-being nexus, it is essential to examine the neural correlates of a diverse set of word categories and their potential interactions.

The categorisation of words into distinct groups provides a framework for understanding their varying impacts on mental health. This approach allows us to dissect the nuanced ways in which different types of words can influence cognitive and emotional processes. Key categories of interest include:

- Cognitive Terms: Words that relate to thinking and reasoning, such as "analyse" and "understand," which are linked to higher-order cognitive functions and are predictive of better mental health outcomes
- Concrete Nouns: Words that refer to tangible objects, like "tree" and "chair," which can ground individuals in the present moment and reduce rumination (Watkins & Moulds, 2005).
- Drive Terms: Words that express behavioural activation, motivation and goal pursuit, such as "strive" and "achieve," which are associated with the brain's reward system and are crucial for resilience and well-being (A way with words: Using language for ...; Tugade and Fredrickson 2004; Pennebaker and King 1999).
- First, Second, and Third Person Pronouns: Words that reflect different perspectives in language use. First-person pronouns ("I," "me") are linked to self-referential processing, while second-person ("you") and third-person ("they") pronouns relate to social interaction and perspective-taking (Berry-Blunt et al., 2021; Carey et al., 2015; Edwards & Holtzman, 2017; Tackman et al., 2019).
- Emotional Valence Words: Positive and negative words that directly influence emotional states. Positive words ("joy," "love") engage reward-related brain regions, while negative words ("sad," "angry") are associated with threat processing (Barr et al., 2008; Dao et al., 2014; Klein & Boals, 2010).
- Temporal Terms: Words that relate to time, including past ("was"), present ("is"), and future ("will"). These terms anchor thoughts in different timeframes and can influence mental health by affecting how individuals focus on their experiences (Brockmeier, 2015; Garcia & Bargh, 2003).
- Social and Lifestyle Terms: Words that highlight social connections and health behaviours, which are integral to wellbeing. Social terms activate regions involved in empathy and community, while lifestyle terms like "exercise" and "diet" reflect priorities that influence health outcomes (M. D. Lieberman et al., 2007).

Each of these categories can illuminate different aspects of mental health and provide insights into the underlying neural mechanisms that support wellbeing (Pennebaker et al. 2003; Moser et al. 2017; Fredrickson and Joiner 2002; Tausczik and Pennebaker 2010; Zimmermann et al. 2017).

Moreover, the use of fMRI in neurolinguistic research has opened new avenues for exploring how language affects the brain in real-time. Functional MRI allows researchers to observe brain activity as participants engage with different linguistic stimuli, providing a window into the dynamic processes that underpin language and cognition. This technique is particularly valuable for investigating how exposure to specific word categories can influence mental states and neural activation patterns, providing objective, physiological data.

Neural imaging lets us see if emotional or motivational words, for instance, activate reward systems, stress circuits, or areas tied to self-regulation—critical elements in understanding the underlying causes of wellbeing or distress. Different individuals may also have unique neural responses to language. Imaging captures this variation, allowing for a more personalised view of language's impact on wellbeing. For example, words linked to achievement might boost wellbeing for one person but trigger stress for another. Only by studying brain function in response to language can we begin to identify such personalised patterns, which could inform more tailored mental health interventions.

For example, emotional words, whether positive or negative, engage the limbic system, a key player in emotion regulation, with positive terms triggering the reward system and negative terms engaging the amygdala in threat processing (Hamann & Mao, 2002; Ishii et al., 2003; Olano et al., 2020). Meanwhile, social words like "friend" and "family" activate regions involved in social cognition and empathy (O'Donnell et al., 2015). Similarly, self-referential words like first-person pronouns activate the MPC and PCC, areas implicated in self-awareness and autobiographical memory (Saxe & Powell, 2006; Uddin et al., 2007). Language related to future planning and goal-setting has been linked to activation in the PFC and striatum, crucial for goal-directed behaviour and reward anticipation (D'Argembeau et al., 2010).

However, the majority of fMRI studies on language processing have relied on highly controlled, artificial stimuli, such as single words or isolated sentences. While these approaches have been instrumental in elucidating the basic mechanisms of language processing, they may not fully capture the complexity and richness of language as it is encountered in real-world contexts (Hasson et al., 2018).

To address this limitation, there has been a growing interest in using naturalistic stimuli, such as movies or narratives, to study language processing in more ecologically valid settings (Finn et al., 2020; Hasson et al., 2010; Lerner et al., 2011). These paradigms involve using complex stimuli like movies or spoken narratives to elicit brain responses that mimic real-world experiences (Saarimäki, 2021). Naturalistic fMRI paradigms offer several advantages over traditional approaches, including enhanced engagement and the ability to investigate the temporal dynamics of brain activity during continuous language processing (Bottenhorn et al., 2019; Hasson et al., 2010).

Recent studies using naturalistic fMRI have provided novel insights into the neural mechanisms underlying language comprehension and its relationship to various cognitive and affective processes (Huth et al., 2016; Nastase et al., 2021). For example, Huth et al., (2016) used fMRI to map the semantic representation of language across the human cerebral cortex while participants listened to hours of natural narrative stories. Their results revealed a complex, hierarchical organisation of semantic information, with distinct cortical regions selective for specific semantic domains.

Similarly, in this study, we leverage the Naturalistic Neuroimaging Database (NNDb), which contains fMRI scans of participants watching movie stimuli (Aliko et al., 2020; Vanderwal et al., 2019). Movies provide a rich, contextually grounded source of language, offering a dynamic and immersive way to study how different words affect the brain (Pinti et al., 2018). The NNDb is one of the largest and most varied naturalistic datasets to date. It hosts a collection of 86 fMRI datasets, both structural and functional, of people watching full-length movies, spanning various genres such as drama, action, and science fiction (Aliko et al., 2020). Previously researchers have used data from the NNDb to investigate various aspects of brain function, such as emotional processing (Klamer et al., 2023a, 2023b), neural synchrony in response to stimuli (Jääskeläinen et al., 2021), and the neural basis of theory of mind (Klamer et al., 2023b). Additionally, the NNDb has been instrumental in exploring the impact of psychological well-being on neural activity (Haines et al., 2023) and studying changes in neural architecture during narrative processing (Wang et al., 2017).

By analysing the scripts of these movies, we can extract words that fall into semantic r categories of interest and correlate them with the fMRI data to uncover how these words are processed in the brain. We can then assess these activation patterns to see whether they have utility in predicting wellbeing. Our study aims to provide a more comprehensive understanding of how different word categories influence brain function and mental well-being. By analysing the neural responses to 16 distinct word categories extracted from movie scripts, we seek to:

- Map Neural Activation: Identify the specific brain regions activated by each word category and understand their roles in cognitive and emotional processing, extending beyond the findings of previous research (Huth et al., 2016).
- Predict Wellbeing Outcomes: Explore how different word categories can predict individual differences in mental health and wellbeing, using fMRI data to identify potential biomarkers.
- Develop Predictive Models of Wellbeing: Leveraging the power of ML techniques (Bzdok & Ioannidis, 2019), and based on neural responses to the selected word categories, construct a model to predict which wellbeing group, high or low, a participant belongs to.
- Inform Therapeutic Approaches: Provide insights that could inform the development of language-based interventions aimed at enhancing mental health.

Methodology

Naturalistic Neuroimaging Database (NNDb)

Overview

The NNDb is an innovative repository aimed at advancing the study of brain function through ecological stimuli, i.e. watching movies. Traditional neuroimaging often relies on reductionist and artificial tasks, such as isolated images or sounds, which do not reflect the complexity of everyday experiences. In contrast, the NNDb provides a rich set of fMRI data collected from participants watching full-length movies, allowing researchers to explore brain activity in more realistic contexts. This approach bridges the gap between controlled experimental settings and the naturalistic scenarios our brains navigate daily, making it ideal for investigating the neural correlates of wellbeing and language use, as the main facets addressed in this thesis.

Participants

The database contains datasets from 86 human participants (42 females, age range 18–58 years, *M* = 26.81, *SD* = 10.09 years) who underwent the NIH Toolbox and then watched one of 10 full-length movies during fMRI brain activity recording. The participants were all right-handed, native English speakers, with no history of neurological/psychiatric illnesses, no hearing impairments, unimpaired or corrected vision and taking no regular medication.

Movie stimuli

The movies used in the NNDb were selected to cover a broad range of genres and emotional tones, ensuring that the data captured a wide spectrum of neural responses. These included:

- 12 Years a Slave (Historical, 7715 seconds).
- 500 Days of Summer (Romance, 5470 seconds).
- Back to the Future (Sci-fi, 6674 seconds).
- Citizen Four (Documentary, 6804 seconds).
- Little Miss Sunshine (Comedy, 5900 seconds).
- Pulp Fiction (Action, 8882 seconds).
- Split (Horror, 6739 seconds).
- The Prestige (Thriller, 7515 seconds).
- The Shawshank Redemption (Drama, 8181 seconds).
- The Usual Suspects (Crime, 6102 seconds).

The movies were presented to participants in full screen through a mirror reversing LCD projector to a rear-projection screen measuring 22.5 cm x 42 cm with a field of view angle of 19.0°. The screen was placed at the back of the MRI bore and was reflected through a mirror above the participants' eyes. High quality audio was presented in stereo via a Yamaha amplifier through Sensimetrics S14 scanner noise-attenuating insert earphones (https://www.sens.com/products/model-s14/).

Cognitive and Behavioral Testing

To complement the neuroimaging data, each participant's cognitive abilities were assessed for over one hour using the NIH Toolbox, which includes a range of tests for memory, attention, and executive function. These tests provide a detailed cognitive profile that can be linked to neural responses observed during the movie-watching sessions.

Procedure

As originally reported and in more depth in Aliko et al. (2020), participants attended two sessions on two separate days 2-4 weeks apart. The NIH toolbox was administered in session one. During session 2, participants watched the movie while undergoing functional and anatomical scans in the fMRI scanner, and an additional questionnaire on the viewed movie. MRI-safe glasses were given to participants with less than perfect vision and, alongside noise attenuating headphones, participants got to choose an earbud size that was most comfortable for them. Also for comfort and to reduce movement, participants were placed in the head-coil with pillows under the head, covering the ears and under the knees during the scans. They were instructed to move as little as possible, and then given a bulb in their right hand that they could squeeze if they required any assistance during the scan.

fMRI scans contained on to three breaks dependent on the length of the movie, with the longer movies having more breaks. In these breaks, participants were instructed to relax but not move. There was a camera placed over the left eye of participants to ensure that we could communicate to participants if they appeared drowsy or uncomfortable. Following the movie, an anatomical scan was collected, and outside of the scanner, participants completed a final questionnaire on the movie they had watched. They were then paid and left.

Data

The dataset includes both fully pre-processed structural (high-resolution T1-weighted anatomical scans) and functional scans (up to 6 fMRI runs), enabling a comprehensive examination of brain activity and its underlying anatomical structures during dynamic and engaging stimuli.

Acquisition

Functional and anatomical images were acquired on a 1.5T Siemens MAGNETOM Avanto with a 32-channel head coil (Siemens Healthcare, Erlangen, Germany). Multiband EPI (Feinberg et al., 2010) (TR = 1 s, TE = 54.8 ms, flip angle of 75°, 40 interleaved slices, resolution = 3.2 mm isotropic) was used, alongside 4x multiband factor and no in-plane acceleration; to reduce cross-slice aliasing (Todd et al., 2016), the 'leak block' option was enabled (Cauley et al., 2014). Although some parts of the cerebellum were missed due to some individuals having larger heads, slices were manually obliqued to cover as much of the brain as possible. The EPI sequence had a software limitation of one hour of consecutive scanning, therefore each movie had at least one break. Between 5,470 and 8,882 volumes were collected per participant, depending on the movie (see Aliko et al (2020), Table 1). A 10 min high-resolution T1-weighted MPRAGE anatomical MRI scan followed the functional scans (TR = 2.73 s, TE = 3.57 ms, 176 sagittal slices, resolution = 1.0 mm)[3].

Preprocessing

More detailed preprocessing stages are listed in Chapter 4, wherein I preprocessed the files directly myself. But, as mentioned, these preprocessing stages are in accordance with Aliko et al., (2020). AFNI was used in all stages of the preprocessing pipeline using the standard afni_proc.py approach as detailed in Cox et al., (1996). A brief overview is described below separately for the anatomical and functional scans.

Anatomical

First of all, the anatomical scan was corrected for image intensity non-uniformity with AFNI's 3dUniformize command and deskulled using ROBEX (Iglesias et al., 2011). The image was then nonlinearly aligned to the MNI N27 template brain using the auto_warp.py script (Holmes et al., 1998). Using default Freesurfer parameters (version 6.0, http://www.freesurfer.net) (Destrieux et al., 2010; Fischl, 2012), the anatomical scan was registered. For anonymity, the resulting images were 'defaced' (https://github.com/poldracklab/pydeface).

Functional

Firstly, 3dTshift was used to correct the fMRI time series for slice-timing differences followed by 3dDespike to despike the data. Moreover, 3dvolreg was utilised to align each timepoint to the mean functional image of the centre time series. For 23 participants, the initial localiser scans had to be redone since the participant moved, causing the top slice of the brain to be lost, therefore 3dresample was used on these participants to ensure all functional grids had the same 'xyz' extent. Then, for all 86 participants, the functional data was aligned to the anatomical images with the align_epi_anat.py script. In order to align the data to the MNI space, 3dNwarpApply was used.

3dBlurToFWHM (Friedman et al., 2006) was then used to achieve a level of 6mm full-width half maximum followed by normalisation. Lastly, 3dTproject detrended all regressors, with the first set being commonly used(Caballero-Gaudes & Reynolds, 2017): 1) Legendre polynomials whose degree varied with run lengths (following a formula of [number of timepoints * TR]/150);

2) Six demeaned motion regressors from the volume registration; 3) A demeaned white matter activity regressor from the averaged time series in white matter regions; and 4) A demeaned cerebrospinal fluid regressor from the averaged time series activity in ventricular regions. ICA artefacts were manually selected from the second set.

Timing correction

Due to the movie pausing, timing correction had to be conducted. This was done by introducing a 100 ms delay for each break. Specifically, 3dTshift was used to shift the time series back. Because of this, there was some missing data in the time series, and consequently a TR needed to be added by retrieving the last timepoint of the run and the first timepoint after the movie was stopped and averaging. Therefore, the next run was shifted back by this amount, making the time series continuous.

Data Quality

The NNDb prides itself on high-quality data, characterised by good signal-to-noise ratios (SNRs), minimal movement artefacts, and accurate alignment between the movie's timeline and the fMRI time series. Various data-driven analyses, such as intersubject correlation (ISC) and ICA, have demonstrated the robustness of the data. These techniques confirm that the neural responses are consistent and synchronised across participants watching the same movies. Spatial independent component analysis (ICA) is a powerful tool for detecting and removing artefacts that substantially improves signal-to-noise ratio in movie naturalistic-fMRI data (Liu et al., 2019).

In this instance, the time series was concatenated after subsequent detrending for motion and white matter/cerebrospinal fluid regressors and after timing correction. A spatial ICA was conducted on the time series with 250 dimensions using melodic (version 3.14) from FSL (Smith et al., 2013). As demonstrated by Griffanti et al., (2017), the time series was manually labelled with artefacts removed. After this, 3dTproject was used to concatenate the time series.

Annotations

The dataset is meticulously annotated, with detailed information on participant demographics, behavioural responses, and precise timing of movie events and corresponding brain activity. I annotated classes of words (see below), and there also includes word and face recognition within the movies, which can be used to label neural networks and link brain activity to specific cognitive and emotional processes, as well as analysing how specific stimuli are processed in the brain over time. These annotations were generated using automated tools like Amazon Transcribe and Amazon Recognition. The .wav audio track extracted from the movie was input into Amazon Transcribe, a ML based speech-to-text transcription tool from Amazon Web Services (AWS; https://aws.amazon.com/transcribe/). Word annotations from this were then aligned with subtitle tracks to ensure the utmost accuracy using Dynamic Time Warping (DTW). While Amazon Recognition was used with face annotations to identify and timestamp faces throughout the movies. More information on how I derived word category annotations are described below.

For this thesis, a simple Python script was used to iterate through the movie transcripts, extracting the terms of interest, their start times and duration. Word frequency of each word was then calculated using the wordfreq Python library (Speer, 2022). Another Python script was used to match each term of interest with a neutral matched control on similar duration and word frequency, ensuring no overlap between categories or matches. The other words annotation was then created by subtracting each term and their match from the initial transcript.

Across all of the movies, there were a total of 5101 concrete words, 3331 cognitive words, 1901 drive words, 3042 first person words, 530 future tense words, 1639 lifestyle words, 747 negation words, 396 negative words, 1683 past tense words, 2968 perception terms, 1465 physical terms, 336 positive words, 1700 present tense words, 4368 second person words, 3987 social words and 1428 third person words. For a full breakdown see Table S3.

Analytical Techniques

Data Analysis

The NNDb supports a range of analytical techniques tailored to the complex nature of the data:

- General Linear Model (GLM): Used to identify brain regions activated by specific stimuli or tasks. This was done as a first stage in the current thesis.

And, although, due to time constraints, I could not run the below analyses techniques, they can be applied in future:

- Connectivity Analysis: Examines functional connectivity between brain regions, both during tasks and at rest.

- Multivariate Pattern Analysis (MVPA): Explores patterns of brain activity across multiple voxels to decode cognitive states.
- Dynamic Causal Modelling (DCM): Investigates how different brain regions interact over time during naturalistic tasks.

Applications and Research Opportunities

The NNDb is a versatile tool that supports a wide range of research applications:

- Neuroscience: By analysing how the brain processes complex, naturalistic stimuli, researchers can gain insights into the network organisation and functional dynamics of the brain in more ecologically valid settings than traditional, reductionist paradigms allow.
- Clinical Research: The naturalistic nature of the NNDb's data makes it particularly valuable for identifying possible biomarkers and neural signatures associated with mental health conditions. For example, this current study explores language as one of those biomarkers.
- ML and Computational Neuroscience: The extensive and richly annotated dataset is ideal for training ML models aimed at predicting brain activity patterns based on visual and auditory input from the movies, as done in this thesis. Such models can enhance our understanding of brain function and contribute to the development of neurotechnology applications.

Applications of NNDb in This Study

Research Questions

The primary research questions addressed using the NNDb in our study include:

- Which areas of the brain show activity depending on the word category? Specifically, how does activation in specific brain areas correspond to different lexical categories?
- Do specific word categories correspond to health and wellbeing?
- Can these be used to classify subjects into high or low wellbeing groups?

Hypotheses

Based on the rich, naturalistic data from NNDb, and prior research, we hypothesise that each word category is processed and comprehended uniquely throughout the brain, in that brain regions beyond the typical static “language regions” show activity depending on the word category.

For instance, we hypothesise that abstract cognitive terms will show activity in the left IFG, PFC, especially areas linked to higher-order thinking, such as the dorsolateral PFC (involved in working memory) (D'Esposito 2000) and the ACC (linked to decision-making and problem-solving) (Bush et al. 2000) while concrete terms activate the anterior FG and bilateral occipital-temporal areas, including the left FG and AG, reflecting their reliance on sensory information (Binder et al. 2009; Wang et al. 2010; Del Maschio et al. 2021). Drive terms will show activity in the ACC and insula, areas involved in emotion regulation and reward processing (Craig 2009; Craig 2009; Etkin et al. 2011), and activate the hypothalamus and limbic system, particularly regions associated with motivation and survival, such as the amygdala and orbitofrontal cortex, due to their connection with basic needs (LeDoux 2007; Kringelbach and Rolls 2004). However, since this study is the first of its kind, these hypotheses are mainly exploratory.

Depending on perspective, pronouns will be processed differently, i.e. first-person pronouns engage the medial prefrontal cortex (mPFC) and PCC, which are part of the DMN and are linked to self-referential thinking, second-person pronouns activate regions such as the TPJ and ventromedial PFC, important for theory of mind (TOM) and understanding others' perspectives, and third-person pronouns activate the posterior superior temporal sulcus (pSTS) and dorsomedial PFC, involved in social perception. Likewise, temporal words will also differ in their activity patterns, i.e. future words activate the dorsolateral prefrontal cortex (DLPFC), ventromedial prefrontal cortex (vmPFC) and hippocampus, both involved in planning and future thinking, while past tense words engage regions such as the hippocampus and PCC, important for memory retrieval, and present tense words are processed mainly in the sensorimotor and premotor cortex due to their immediacy and connection to current action.

Lifestyle-related terms and physical terms typically engage brain areas related to embodied cognition, such as the premotor cortex and somatosensory areas, as well as the anterior temporal lobe and mPFC, areas associated with personal and social knowledge. Perception words activate sensory association cortices depending on the sensory modality (e.g., visual, auditory), occipital lobe for vision, temporal lobe for auditory processing, and somatosensory cortex for touch.

Negation words and negative terms activate the right IFG, amygdala, ventrolateral PFC and anterior insula, areas tied to emotional processing and evaluation, whereas positive words are associated with activity in the vmPFC, nucleus accumbens and ventral striatum, all regions involved in reward processing and positive affect. Finally, social words broadly activate the TPJ, pSTS, anterior temporal cortex and mPFC due to their role in social cognition.

As a whole, this distributed pattern of brain activity reflects the complexity of language processing, with each category hypothesised to elicit specialised cognitive mechanisms. We then hypothesise that we can use these activation maps to predict wellbeing state based on NIH toolbox scores of subjects.

Linguistic Inquiry Word Count (LIWC)

To identify the most relevant word categories for this study, we will employ the Linguistic Inquiry and Word Count (LIWC) framework, a validated tool for analysing language patterns based on a comprehensive set of linguistic dimensions (*A Way with Words: Using Language for Psychological Science in the Modern Era*, n.d.)). By referencing the LIWC categories, we will select a diverse set of word groups with potential relevance to mental wellbeing, including cognitive terms, emotional terms, social terms, and temporal terms, among others.

Developed by (Tausczik & Pennebaker, 2010), LIWC provides a robust framework for categorising linguistic expressions across various research fields. Researchers have utilised LIWC to explore the intricate relationship between language use and emotional experiences. These linguistic markers not only provide a glimpse into individuals' emotional landscapes but also contribute to understanding the cognitive processes associated with wellbeing.

LIWC works by checking each word against its internal dictionary of over 2300 words and word stems, assigning them to specific linguistic categories. While we looked at all of the possible LIWC categorisations, we opted to focus on sixteen main categories of interest that were most central to our hypotheses. These comprised of: cognitive, concrete, drive, first person, future, lifestyle, negation, negative, past, perception, physical, positive, present, second person, social and third person terms.

We used the LIWC2015 internal English dictionary. Cognitive terms comprised 797 wordforms and patterns, including “cause”, “know”, and “ought.” Drive-related terms included 1103 wordforms and patterns, such as “ally,” “win,” “superior,” “take” and “danger.” First person singular pronouns consisted of the words “I,” “me,” and “mine,” second person with “you,” “your,” and “thou,” and third person with “she,” her” and “him.” Future tense comprised of 97 wordforms and patterns, i.e. “may,” “will” and “soon,” while past tense comprised of 341 wordforms and patterns, i.e. “ago,” “did,” and “talked,” and present tense comprised of 424 wordforms and patterns, i.e. “today,” “is” and “now.” Lifestyle (“job,” “cook,” “kitchen,” “audit,” “altar,” “bury), perception (“look,” “heard,” “feeling”), physical (“eat,” “blood,” “pain”), social (“mate,” “talk,” “boy”) were made up of 1314, 436, 748 and 756 wordforms and patterns, respectively. The positive emotion category consisted of 620 wordforms and patterns, e.g. “love,” “nice” and “sweet,” whereas the negative emotion category was made up of 744 wordforms and patterns, e.g. “hurt,” “ugly” and “nasty.” Similarly, negation terms consisted of 62 wordforms and patterns, mostly being “no,” “not” and “never.” In terms of patterns, ‘*’ are included within the dictionary which matches any wordform that starts identically. For instance, “negativ*” would match both “negative” and “negativity.”

First Level Analysis

In the current study, The GLM was applied to the preprocessed fMRI data using the AFNI program 3dDeconvolve to first estimate the voxel-wise response amplitudes with the standard canonical hemodynamic response function (HRF). This multiple regression program calculates the impulse response function by relating the fMRI time series data to the timing of the stimulus onset and duration. Regressors included the 16 word categories known to predict health and wellbeing, paired with neutral control words matched for similar duration and frequency (see Table S3 for a full breakdown), and all other words. The GLM, therefore, had 48 contrasts, with each word being compared with the matched word and all other words. Overall, this analysis provided the brain activation associated with each condition.

Group-Level Analysis

Voxel-wise group differences were first analysed using AFNI’s 3dttest++ program. In a paired approach, subbricks were taken from the statistical output of the first level analysis denoting to the word category and their match. The procedure included computing residuals, generating a null distribution through randomisation, and iterating the t-tests 10,000 times to determine the cluster-size threshold for a given false positive rate (FPR). This tool facilitated voxel-wise t-tests while incorporating between-subject factors and covariates such as age and gender. The resulting t-maps were thresholded using ClustSim to control the false positive rate, with a voxel-wise threshold of $p < .001$ and a cluster significance level of $p < .05$ (Cox et al., 2017).

We then used AFNI's 3dLME for whole brain voxel-wise group differences with a simple model summing the condition (word category vs all other words in the movie script, not including previously identified matches and the word from the category) with the covariates for age, gender and task (movie watched). All 3dLMEs included an intercept to remove confounds. The input was the beta coefficient level of the word and other words from the first level analysis. Only clusters identified by 3dLMEs exceeding 40 voxels were considered (uncorrected $P < .01$).

Predictive Modelling

In this study, we explored various classifier training methods in order to see which was most robust and fit the data best, with classifier being defined as a function which takes a set of examples and outputs a binary class label to each (in this case 0 or 1), including Logistic Regression (LR), Support Vector Machine (SVM), Random Forest (RF), and Convolutional Neural Network (CNN). These classifiers were selected due to their successful application in prior studies, particularly in handling high-dimensional data (Yeung et al., 2023).

The inputs to the models were the intensity normalised T2-weighted and T1-weighted entire images for each patient and a true class binary vector with the information on wellbeing (0 = low wellbeing, 1 = high wellbeing). These values were calculated by using a composite of relevant wellbeing score from the NIH toolbox, i.e. the psychological wellbeing pack, with any score >50 denoting high wellbeing and any scores <50 denoting low wellbeing. The output of the algorithm was a probability value for each participant of belonging to 1 of the 2 classes: low or high wellbeing.

To clarify, the SVM model is designed to predict an individual's level of psychological wellbeing based on their responses to the NIH Toolbox Psychological Well-Being Index. This index comprises several subdomains, including General Life Satisfaction, Emotional Support, Loneliness, Perceived Stress, and Self-Efficacy.

In our model, ‘high’ wellbeing is characterised by high scores in General Life Satisfaction, Emotional Support, and Self-Efficacy, combined with low scores in Loneliness and Perceived Stress. Conversely, ‘low’ wellbeing is defined by the opposite pattern: low scores in General Life Satisfaction, Emotional Support, and Self-Efficacy, coupled with high scores in Loneliness and Perceived Stress.

As described below, we fitted four different models to the data, which is commonplace in computer science, particularly machine learning work, in order to capture different patterns or relationships in the data, which helps avoid making assumptions that could limit the robustness or generalisability of the results. By evaluating multiple models, we gain insights into how different algorithms handle the data structure, and the trade-offs in complexity, interpretability, and performance across models.

Logistic Regression (LR)

Logistic Regression was chosen as a baseline classifier for its simplicity and effectiveness in binary classification problems, particularly when the relationship between the input features and the output class is approximately linear (Hosmer et al., 2013). We implemented the LR model using the scikit-learn library in Python (Pedregosa et al., 2011). Given its linear nature, LR is less prone to overfitting compared to more complex models, especially when the number of features is relatively small.

The model was trained using the entire feature set, and regularisation was applied to prevent overfitting, with the regularisation strength (C) parameter tuned through grid search (Bergstra & Bengio, 2012; Cong et al., 2018). Regularisation was particularly important to prevent overfitting, especially given the high dimensionality of neuroimaging data (Cong et al., 2018). The final model was evaluated using a leave-one-out cross-validation (LOO-CV) approach, ensuring robust performance estimation.

The voxel-wise beta coefficients from the prior GLM analysis of each word category were used as predictors, with the binary wellbeing category (high wellbeing = 1, low wellbeing = 0) as the outcome variable, based on NIH toolbox scores of the aforementioned 86 participants of the NNDb database. The dataset was split into training (70%) and testing (30%) sets. The LR model was trained on the training set and validated on the testing set to assess its predictive accuracy.

Cons of the logistic regression model, however, mainly include that the data needs to be linear, oversimplifying multivariate interactions, and this model is also less capable of capturing interactions between features compared to more complex models (described below). Using logistic regression provides a baseline that's easy to interpret, making it useful for comparison with the more complex models. It helps establish whether the task requires a more sophisticated approach.

Support Vector Machine (SVM)

SVMs were fit using scikit-learn's support vector machine (SVM) (Pedregosa et al., 2011). The SVM model allowed for capturing more complex multivariate relationships within the data. Though, given the relatively small sample size (*N* = 86), we opted for an SVM classifier with a linear kernel, which is effective in small datasets by generating a decision boundary that maximises separation between wellbeing states (Arslan et al., 2016; Chennu et al., 2017; Sitt et al., 2014). Hyperparameter tuning was conducted to optimise model performance (Bzdok & Ioannidis, 2019), alongside a previously mentioned LOO-CV.

SVMs are computationally intensive, especially with the volume of data in this study, and, thus, took time and resources to run, as well as additional time to find the best tuning parameters. However, SVMs are known for strong performance in classification tasks and, therefore, could capture meaningful patterns in this categorical data.

Random Forest (RF)

For Random Forest, again created with scikit-learn (Pedregosa et al., 2011), a subtype of decision trees, we constructed multiple trees using bootstrap samples from the original data. This ensemble approach, known as bagging, reduces model variance and mitigates overfitting, improving generalisation to new data (Altman & Krzywinski, 2017). Hyperparameters, such as the number of decision trees, were tuned via grid search to optimise model performance (Bergstra & Bengio, 2012), and the best-performing parameters were applied to the final model, which was tested again using the LOO-CV approach. During each LOO-CV iteration, the training data were scaled, and the corresponding transformation was applied to the test dataset.

RF's ensemble nature helps mitigate overfitting, giving clear interpretations and strong predictive power. However, a disadvantage of RF is that they can be less effective for high-dimensional data without significant feature engineering, which was too time consuming to conduct entirely for the scope of this thesis.

Convolutional Neural Network (CNN)

For the Convolutional Neural Network (CNN), the model was constructed using TensorFlow and Keras, a popular deep learning framework (Abadi, 2016; Kapoor et al., 2022). CNNs are well-suited for handling structured data, particularly in domains like image and signal processing, by capturing local patterns through convolutional layers. The architecture used in this study consisted of multiple convolutional layers followed by pooling layers, which progressively reduced the spatial dimensions and highlighted the most salient features of the input data (Lecun et al., 1998).

The model architecture was fine-tuned based on validation performance, with key hyperparameters such as the number of filters, filter sizes, and the number of fully connected layers being adjusted through a combination of grid search and manual experimentation. Overall, the CNN model consists of 2 convolutional layers and 2 fully-connected layers (with 128 and 2 neurones, respectively). The numbers of channels in the convolutional layers are 32 and 64, respectively, and the convolution kernel sizes are both 3 x 3 x 3.

A rectified linear unit (ReLU) activation function was applied in each layer to introduce non-linearity, which is crucial for learning complex patterns in the data (Nair & Hinton, 2010), followed by max-pooling layers to downsample the data. The final output layer used a softmax activation function to convert the CNN outputs into class probabilities, enabling multiclass classification. Additionally, dropout was applied to prevent overfitting during the training process (Srivastava et al., 2014).

Training of the CNN was conducted using a mini-batch gradient descent with the Adam optimiser, chosen for its computational efficiency and adaptive learning rate capabilities (Kingma & Ba, 2014). Given the relatively small sample size, data augmentation techniques were employed to artificially increase the diversity of the training set, thereby reducing the risk of overfitting (Shorten & Khoshgoftaar, 2019). The number of epochs was set to 30, and the batch size was 64, resulting in 126,990 iterations. The model's performance was evaluated using LOO-CV, ensuring that each data point contributed to the model's validation while maximising the use of available data.

Although CNNs are the most powerful model used in this research, especially given complex imaging data, they are prone to overfitting in the cases of limited data without careful, time consuming regularisation and tuning. Since the UNITy dataset (Chapter 4) is very limited in terms of data, we decided to proceed with the simpler, less intensive SVM model.

Statistical Analysis

The SVM coefficients were mapped onto brain images to identify the brain regions most associated with high and low wellbeing. Positive coefficients indicated regions where higher activation increased the probability of high wellbeing, while negative coefficients indicated the opposite. This visualisation displayed distinct patterns of neural activation across the brain. Positive coefficients (red areas) indicated brain regions positively correlated with high wellbeing, while negative coefficients (blue areas) indicated regions inversely correlated. High absolute coefficients were the most influential in distinguishing between the different wellbeing classes, providing insights into the neural substrates associated with wellbeing.

Model Evaluation

The performance of the models were evaluated using several metrics:

- Accuracy: The proportion of correctly classified instances.
- Sensitivity (recall): The ability of the model to identify true positives (high wellbeing).
- Specificity (precision): The ability of the model to identify true negatives (low wellbeing).
- Area Under the Receiver Operating Characteristic Curve (AUC): A measure of the model's discriminative ability.

Below, an example confusion matrix is shown, illustrating the equations for accuracy, specificity (precision) and sensitivity (recall), courtesy of (Ma et al., 2019):

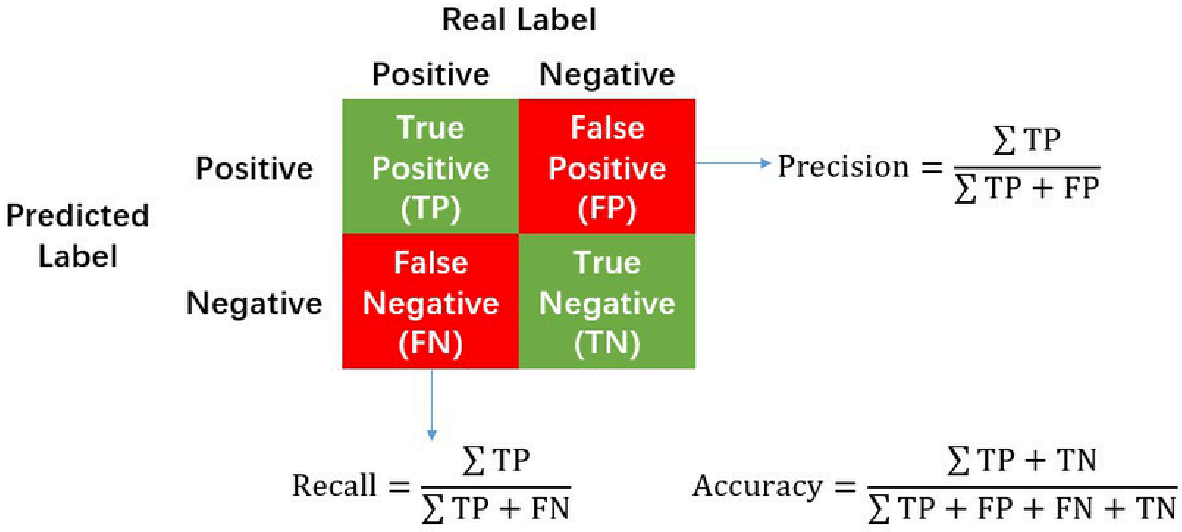


Figure 10. An example of a confusion matrix, from Ma et al., (2019), which highlights the evaluative metrics used on the models.

True positive (TP) equates to high wellbeing participants correctly identified as high wellbeing, false positive (FP) is low wellbeing participants incorrectly identified as high wellbeing, false negative (FN) is high wellbeing participants incorrectly identified as low wellbeing and true negative (TN) is low wellbeing participants correctly identified as low wellbeing. From this, the confusion matrix and the ROC curve were generated to visualise the model's classification performance.

Results

Ttest

The 3dttest+ output produces maps of significant activations for each category, identifying brain regions where the response to the target words differs from the control condition (Figure 7). The output includes both positive and negative t-values, indicating regions of increased or decreased activation, respectively, in response to the word categories.

Overall, when p = 0.01 with a cluster extent threshold of 40 voxels, the analysis revealed distinct patterns of activation across several brain regions. These activations were primarily observed in the temporal, occipital, and frontal lobes, with notable involvement of the precuneus, cuneus, AG, and insula.

Across multiple categories, including concrete, cognitive, drive, lifestyle, negation, negative, past, perception, positive, present, second and third person words, significant activations were observed in the temporal and occipital lobes, regions typically associated with overall language processing, social cognition, and visual processing (Figure 7). For example, the left and right MTG were frequently activated across the categories, with notable positive activations for lifestyle words (x = −60, y = −12, z = −14, 304 voxels; x = 56, y = −2, z = −16, 169 voxels) while past tense words activated a similar region (x = −56, y = 4, z = −20, 634 voxels) and less activity for present (x = −56, y = 8, z = −4, 129 voxels) and negative words (x = −48, y = −56, z = −2, size: 126; x = 46, y = −50, z = 0, 52 voxels), respectively. The MTG was also engaged negatively during the processing of negation (x = −64, y = −52, z = −12, 102 voxels), indicating a bilateral involvement of the temporal regions in language processing.

Similarly, the left FG, linked with visual word form processing, also showed significantly less activity in response to negative words (x = −26, y = −56, z = −12, 360 voxels), while the right FG showed more activity during first-person word processing (x = 56, y = −2, z = 28, 124 voxels). In addition, the left superior occipital gyrus showed less activity for negative words (x = −16, y = −84, z = 40, 118 voxels), and the middle occipital gyrus was engaged during the processing of past tense words (x = −48, y = −72, z = 8, 93 voxels) and less so with third person (x = 48, y = −76, z = 12, 111 voxels).

It is of note that across several categories, including cognitive, negative, and future words, a consistent pattern of negative activity emerged in occipital and temporal regions. For example, negative words elicited significant negative activation throughout the brain, though mostly in the left fusiform gyrus (x = −26, y = −56, z = −12, size: 360 voxels) and the right MTG (x = 46, y = −50, z = 0, size: 52 voxels). Similarly, the left lingual gyrus showed negative activity for both cognitive (x = −14, y = −68, z = −8, size: 113 voxels) and future words (x = 48, y = −60, z = 40, size: 78 voxels).

The frontal lobe and insula were also implicated in processing various word categories. Notably, the left SFG showed positive values in response to lifestyle words (x = −16, y = 36, z = 48, 112 voxels) and past tense words elicited strong activation in the right MFG (x = 52, y = 20, z = 46, 176 voxels), while the left frontal regions and left insula lobe showed less activity for future (x =

−36, y = 24, z = 4, 61 voxels) and positive (x = 64, y = − 4, z = − 2, 144 voxels), respectively. These regions showed less activity with present tense (x = − 38, y = 16, z = 22, 98 voxels).

Moreover, the precuneus and cuneus were prominently engaged across several word categories, comprising social, cognitive, past, future, lifestyle, negative and negation terms. For example, the left precuneus was highly engaged in response to lifestyle words (x = −4, y = −50, z = 36, 467 voxels), while the right cuneus exhibited less activity for negative words (x = 12, y = −96, z = 22, 147 voxels) and for negation words (x = 4, y = −84, z = 34, 49 voxels), and the left precuneus for third person (x = −16, y = −56, z = 22, 323 voxels). The right AG also showed more activity during future word processing (x = −20, y = −68, z = −8, 68 voxels).

Among the various word categories analysed, past tense and lifestyle words evoked the most extensive neural activity, engaging large clusters of brain regions. For instance, as previously noted, past tense words activated the left MTG (x = −56, y = 4, z = −20, size: 634 voxels) and several other regions, indicating robust involvement of both temporal and frontal areas. Lifestyle words also showed widespread activation, particularly in the left precuneus (x = −4, y = −50, z = 36, size: 467 voxels) and the MTG (x = −60, y = −12, z = −14, size: 304 voxels).

These findings suggest that the processing of positive, past tense and lifestyle words engages more extensive and perhaps more complex neural networks than other word categories, making these categories particularly significant for further discussion in subsequent sections. In contrast, categories such as first-person and future words, while still showing notable activity, involved fewer regions and smaller cluster sizes, indicating that they may play a more specific or localised role in language processing.

LME

The 3dLME analyses comparing word categories to all other words, not including matches or the word category (controlling for gender, age, and movie watched; FDR corrected, $p < 0.01$, cluster extent threshold of 40 voxels) revealed significant activations across several brain regions (Figure 7). Regions of more activity for the word category are depicted in red, while regions of less activity for the word category are shown in blue. The “concrete” category was excluded due to no robust activity surviving thresholding.

Foremost, substantial activations were noted in the middle occipital gyrus and MTG, both positively and negatively, across the word categories. For example, first-person words showed less activity in bilateral middle occipital gyrus (right: x = 36, y = −84, z = 20, 295 voxels; left: x = −44, y = −72, z = −2, 126 voxels), and third person words similarly showed less activity in the left middle occipital gyrus (x = −36, y = −84, z = 34, 127 voxels) and more in the right MTG (x = 46, y = −72, z = 16, 698 voxels).

The temporal words (future and past) also resulted in significantly more activation in the left middle occipital gyrus (x = −50, y = −84, z = 0, 332 voxels and x = −50, y = −74, z = 4, 45 voxels, respectively), while present tense words were less associated in the right middle occipital gyrus (x = 32, y = −88, z = 16, 165 voxels).

The calcarine gyrus and lingual gyrus also showed differential activations, with negation words leading to positive activity in the left calcarine gyrus (x = 8, y = −98, z = 10; size = 237 voxels) and negative responses in the bilateral lingual gyrus for first-person words (right: x = 20, y = −50, z = −8; size = 110 voxels and left: x = -14, y = -76, z = -2; size = 87 voxels).

Prefrontal regions revealed variable responses, with future words positively activating the right SFG (x = 16, y = 32, z = 58, 224 voxels) and first- and third-person words deactivating the right IFG (pars opercularis; x = 36, y = 8, z = 32, size = 45 voxels and pars orbitalis; x = 24, y = 36, z = −8, 40 voxels, respectively). Negation words also showed significantly less activity in the left IFG (pars orbitalis; x = −40, y = 36, z = −14, 182 voxels) and insula lobe (x = −40, y = −2, z = −4, 45 voxels).

Additional regions, such as the precuneus, inferior parietal lobule, and parahippocampal gyrus, showed substantial activation across the categories, including less activity in response to positive and negation words in areas like the left hippocampus (x = −28, y = −44, z = −8, 104 voxels). Third-person and second-person words triggered both positive and negative activity in the right (x = 8, y = −50, z = 52, 391 voxels) and left (x = −8, y = −56, z = 0, 34 voxels) precuneus, similar to second-person words (x = −8, y = −56, z = 48, 119 voxels). Future words also positively activated the right precuneus (x = 8, y = −56, z = 56, 54 voxels).

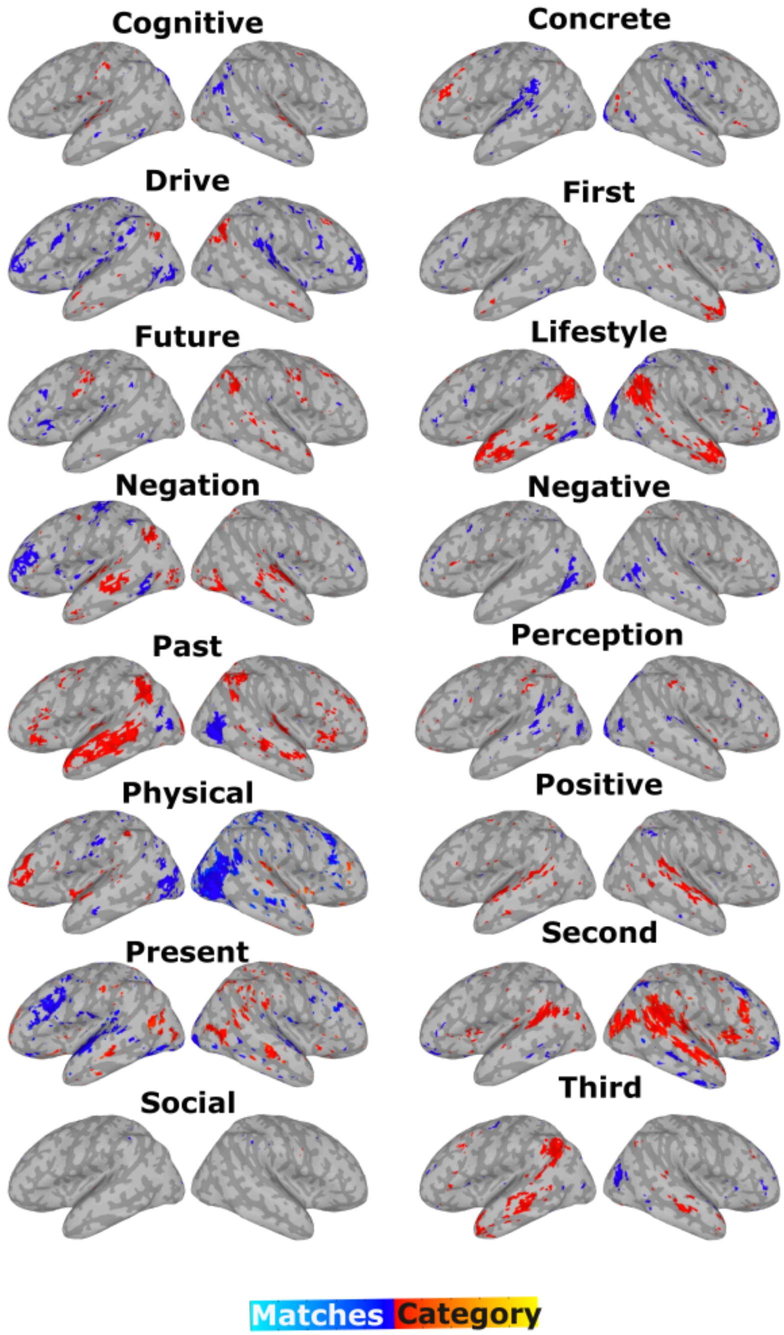


Figure 11. Ttest results of all of the word categories vs matched words on length, frequency and duration ($p < .01$). Red shows areas of increased activity in the word categories when compared to the match while blue shows areas of decreased activity.

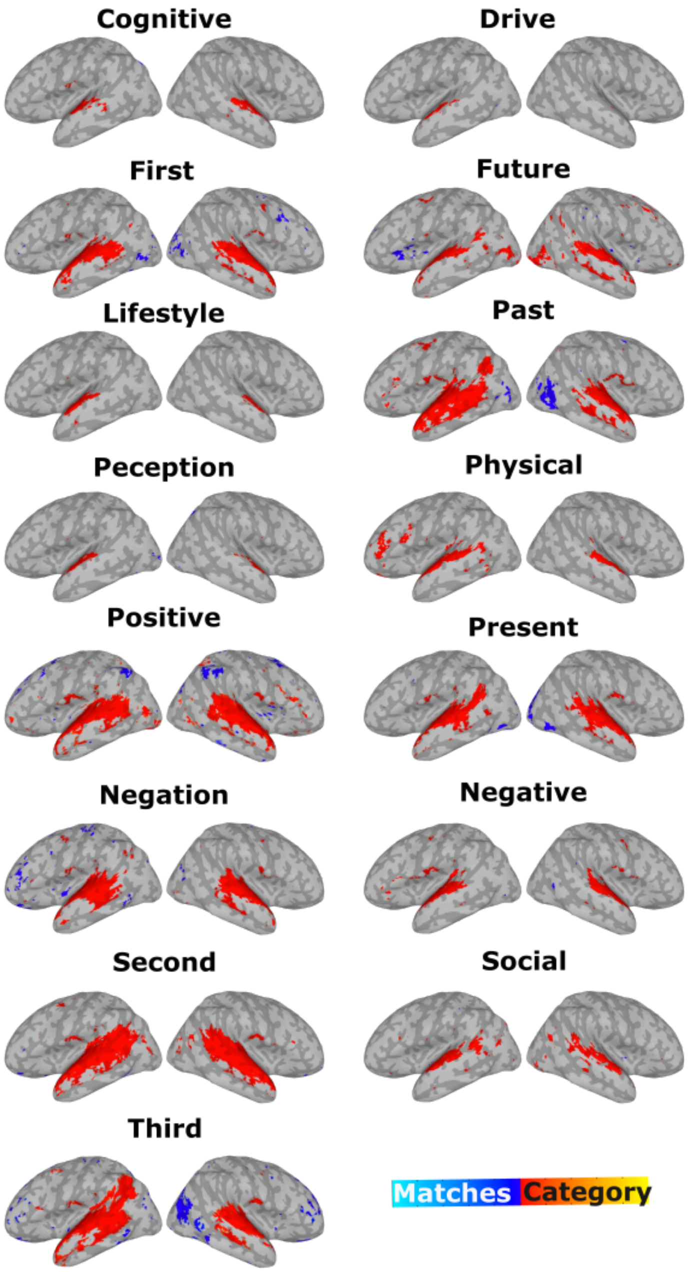


Figure 12. Linear Mixed Effects (LME) model showing Tstat maps of the word categories vs all other words (not including word category and matched control words)($p < .01$, FDR corrected). Red shows areas of increased activity in the word category when compared to the match while blue shows areas of reduced activity.

Classification results

Using the contrast subtraction maps of the word vs the match as an input from the GLM analysis described above, we evaluated the performance of the classifiers using accuracy, sensitivity, and specificity metrics (Tables 6-9). All models showed competitive performance, though with SVM slightly outperforming the majority in terms of accuracy while the RF model provided the most balanced performance, with consistent accuracy, precision, recall, and F1-scores across all categories, making it more reliable overall. The CNN model also showed strong performance, particularly in categories with more balanced data, though it occasionally underperformed in recall compared to RF. Logistic regression, while effective, was less competitive in complex scenarios, especially in recall and F1-score.

The SVM model had higher accuracy than the other models overall, achieving perfect accuracy (1.00) in the lifestyle, physical and third categories, and near-perfect accuracy in the negative (0.99), present (0.99), and social (0.99) categories (Table 7). The CNN model also demonstrated high accuracy, particularly in the future (0.87), lifestyle (0.88), and concrete (0.85) categories (Table 9). The RF model exhibited strong accuracy across most categories, with the highest in social (0.90) (Table8). In contrast, the basic logistic regression model showed lower accuracy, particularly in the negation (0.73) category (Table 6).

However, the SVM model struggled with recall in certain categories, such as drive (0.32 for the high well-being class) and first (0.00 for the high wellbeing class). The RF model provided more balanced precision and recall, performing particularly well in categories like negation (0.96 recall for the high wellbeing class) and physical (0.96 recall for the high wellbeing class). The CNN model showed strong precision and recall across most categories, but its recall in the cognitive (0.62 for the high wellbeing class) and negation (0.79 for the high wellbeing class) categories was lower compared to other models. Logistic regression exhibited the most variability in precision and recall, with lower performance in categories like negation (0.62 recall for the high wellbeing class) and lifestyle (0.68 recall for the high wellbeing class).

In terms of F1-score, the SVM model excelled in the negative (0.99 for the low wellbeing class and 0.98 for the high wellbeing class) and present (0.99 for the low wellbeing class and 0.99 for the high wellbeing class) categories, reflecting its high precision and recall. However, the SVM's F1-scores were notably lower in the drive (0.49 for the high wellbeing class) and first (0.75 for the low wellbeing class and 0.00 for the high wellbeing class) categories due to the significant drop in recall. The RF model achieved balanced F1-scores across categories, with particularly high scores in the past (0.87 for the high wellbeing class) and physical (0.89 for the low wellbeing class) categories. The CNN model also performed well in terms of F1-scores, especially in the future (0.89 for the high wellbeing class) and lifestyle (0.85 for the high wellbeing class) categories. Logistic regression had lower F1-scores in more complex categories like negation (0.65 for the high wellbeing class) and lifestyle (0.71 for the high wellbeing class).

Logistic Regression

Table 6

Performance (accuracy, precision, recall and F1 score) of the logistic regression model.

Category	Accuracy	Precision		Recall		F1-Score	
		Low	High	Low	High	Low	High
Cognitive	0.78	0.79	0.76	0.87	0.65	0.83	0.7
Concrete	0.78	0.8	0.74	0.85	0.68	0.82	0.71
Drive	0.9	0.92	0.86	0.9	0.88	0.91	0.87
First	0.8	0.82	0.77	0.87	0.71	0.84	0.74
Future	0.83	0.82	0.83	0.9	0.71	0.86	0.76
Lifestyle	0.78	0.8	0.74	0.85	0.68	0.82	0.71
Negation	0.73	0.76	0.68	0.81	0.62	0.79	0.65
Negative	0.87	0.85	0.93	0.96	0.74	0.9	0.82
Past	0.88	0.9	0.85	0.9	0.85	0.9	0.85
Perception	0.8	0.8	0.81	0.9	0.65	0.85	0.72
Physical	0.86	0.84	0.89	0.94	0.74	0.89	0.81
Positive	0.86	0.87	0.84	0.9	0.79	0.89	0.82
Present	0.88	0.88	0.9	0.94	0.79	0.91	0.84
Second	0.79	0.77	0.83	0.92	0.59	0.84	0.69
Social	0.84	0.88	0.78	0.85	0.82	0.86	0.8
Third	0.8	0.81	0.79	0.88	0.68	0.84	0.73
Overall	0.82375	0.831875	0.813	0.89	0.724	0.859	0.764

Support Vector Machine (SVM)

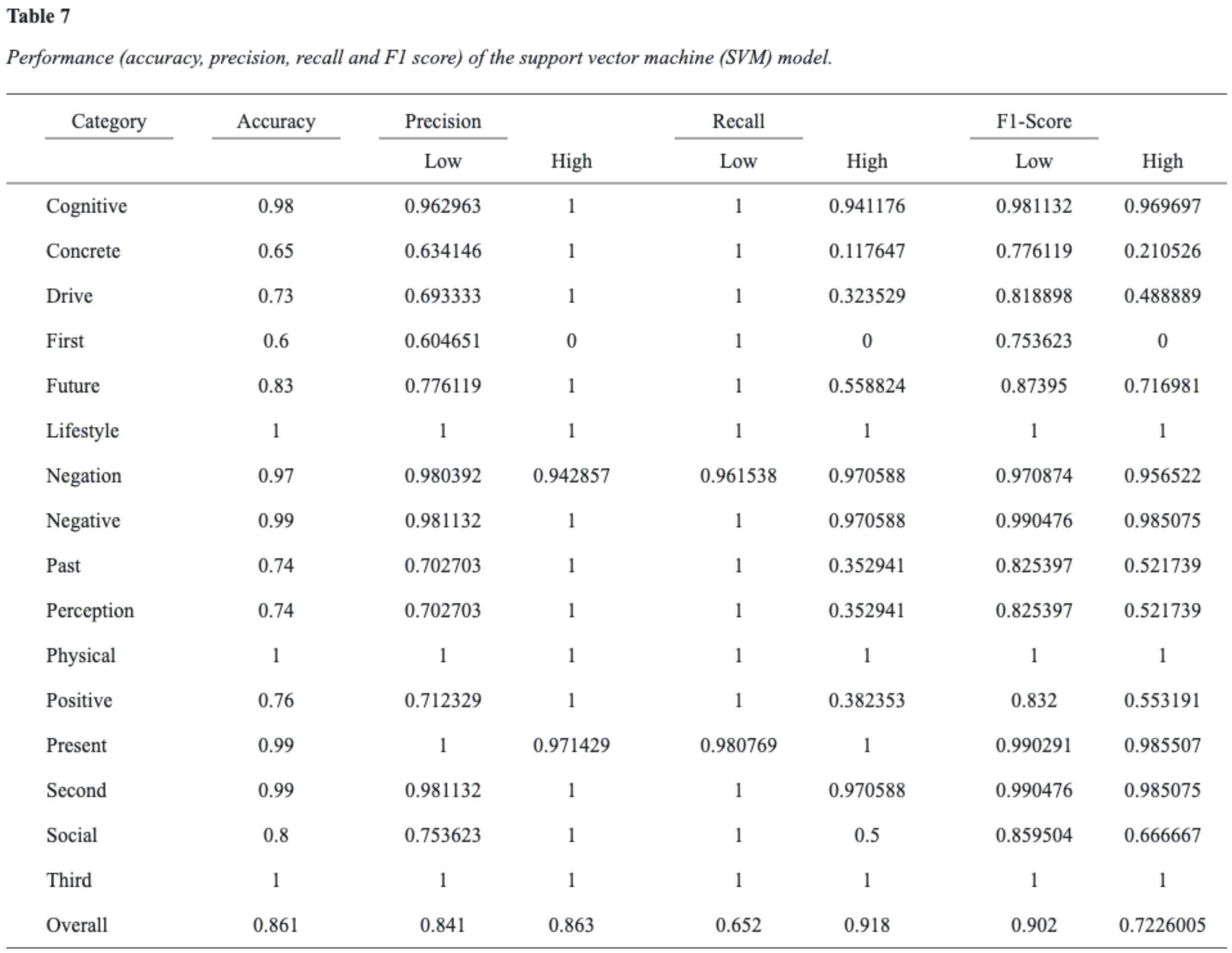


Table 7

Performance (accuracy, precision, recall and F1 score) of the support vector machine (SVM) model.

Category	Accuracy	Precision		Recall		F1-Score	
		Low	High	Low	High	Low	High
Cognitive	0.98	0.962963	1	1	0.941176	0.981132	0.969697
Concrete	0.65	0.634146	1	1	0.117647	0.776119	0.210526
Drive	0.73	0.693333	1	1	0.323529	0.818898	0.488889
First	0.6	0.604651	0	1	0	0.753623	0
Future	0.83	0.776119	1	1	0.558824	0.87395	0.716981
Lifestyle	1	1	1	1	1	1	1
Negation	0.97	0.980392	0.942857	0.961538	0.970588	0.970874	0.956522
Negative	0.99	0.981132	1	1	0.970588	0.990476	0.985075
Past	0.74	0.702703	1	1	0.352941	0.825397	0.521739
Perception	0.74	0.702703	1	1	0.352941	0.825397	0.521739
Physical	1	1	1	1	1	1	1
Positive	0.76	0.712329	1	1	0.382353	0.832	0.553191
Present	0.99	1	0.971429	0.980769	1	0.990291	0.985507
Second	0.99	0.981132	1	1	0.970588	0.990476	0.985075
Social	0.8	0.753623	1	1	0.5	0.859504	0.666667
Third	1	1	1	1	1	1	1
Overall	0.861	0.841	0.863	0.652	0.918	0.902	0.7226005

Random Forest

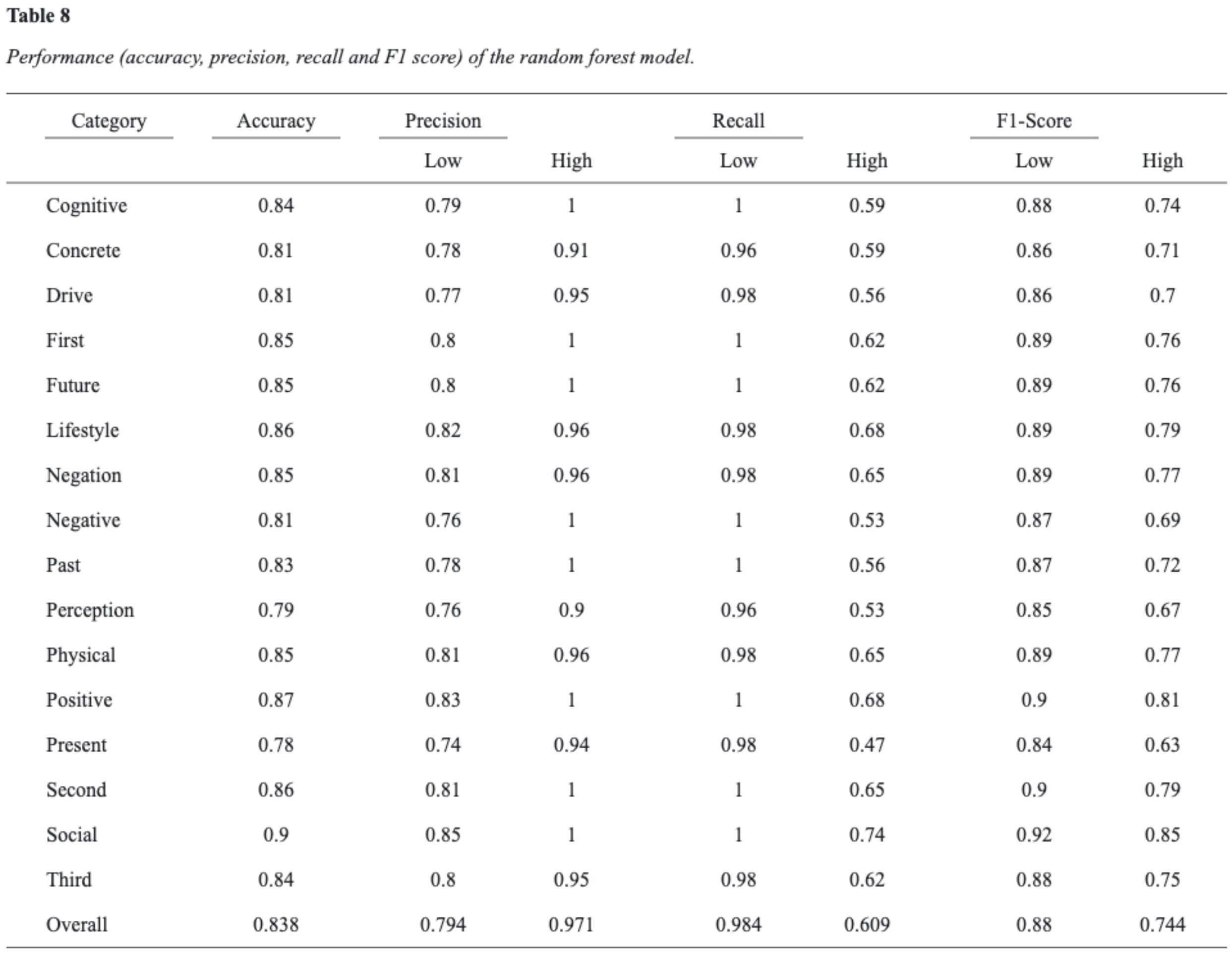


Table 8

Performance (accuracy, precision, recall and F1 score) of the random forest model.

Category	Accuracy	Precision		Recall		F1-Score	
		Low	High	Low	High	Low	High
Cognitive	0.84	0.79	1	1	0.59	0.88	0.74
Concrete	0.81	0.78	0.91	0.96	0.59	0.86	0.71
Drive	0.81	0.77	0.95	0.98	0.56	0.86	0.7
First	0.85	0.8	1	1	0.62	0.89	0.76
Future	0.85	0.8	1	1	0.62	0.89	0.76
Lifestyle	0.86	0.82	0.96	0.98	0.68	0.89	0.79
Negation	0.85	0.81	0.96	0.98	0.65	0.89	0.77
Negative	0.81	0.76	1	1	0.53	0.87	0.69
Past	0.83	0.78	1	1	0.56	0.87	0.72
Perception	0.79	0.76	0.9	0.96	0.53	0.85	0.67
Physical	0.85	0.81	0.96	0.98	0.65	0.89	0.77
Positive	0.87	0.83	1	1	0.68	0.9	0.81
Present	0.78	0.74	0.94	0.98	0.47	0.84	0.63
Second	0.86	0.81	1	1	0.65	0.9	0.79
Social	0.9	0.85	1	1	0.74	0.92	0.85
Third	0.84	0.8	0.95	0.98	0.62	0.88	0.75
Overall	0.838	0.794	0.971	0.984	0.609	0.88	0.744

Convolutional Neural Network

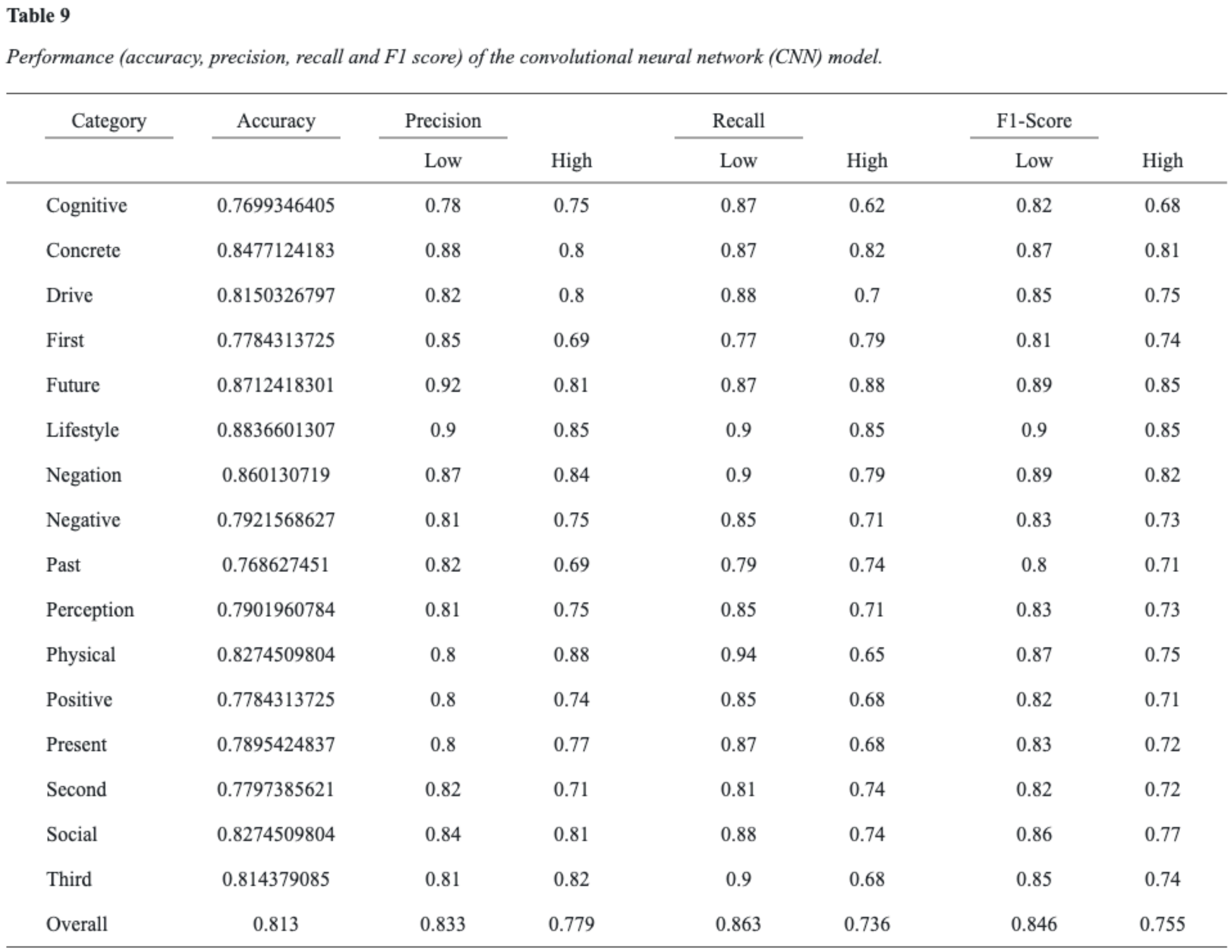


Table 9

Performance (accuracy, precision, recall and F1 score) of the convolutional neural network (CNN) model.

Category	Accuracy	Precision		Recall		F1-Score	
		Low	High	Low	High	Low	High
Cognitive	0.7699346405	0.78	0.75	0.87	0.62	0.82	0.68
Concrete	0.8477124183	0.88	0.8	0.87	0.82	0.87	0.81
Drive	0.8150326797	0.82	0.8	0.88	0.7	0.85	0.75
First	0.7784313725	0.85	0.69	0.77	0.79	0.81	0.74
Future	0.8712418301	0.92	0.81	0.87	0.88	0.89	0.85
Lifestyle	0.8836601307	0.9	0.85	0.9	0.85	0.9	0.85
Negation	0.860130719	0.87	0.84	0.9	0.79	0.89	0.82
Negative	0.7921568627	0.81	0.75	0.85	0.71	0.83	0.73
Past	0.768627451	0.82	0.69	0.79	0.74	0.8	0.71
Perception	0.7901960784	0.81	0.75	0.85	0.71	0.83	0.73
Physical	0.8274509804	0.8	0.88	0.94	0.65	0.87	0.75
Positive	0.7784313725	0.8	0.74	0.85	0.68	0.82	0.71
Present	0.7895424837	0.8	0.77	0.87	0.68	0.83	0.72
Second	0.7797385621	0.82	0.71	0.81	0.74	0.82	0.72
Social	0.8274509804	0.84	0.81	0.88	0.74	0.86	0.77
Third	0.814379085	0.81	0.82	0.9	0.68	0.85	0.74
Overall	0.813	0.833	0.779	0.863	0.736	0.846	0.755

Lastly, heatmaps with an absolute value of 0.2 and corrected with FDR were generated to visualise the most relevant voxels contributing to classification decisions. The locations of the voxels that underpinned the accurate wellbeing classification (i.e. the diagnostic voxels) were similar and consisted mainly of bilateral STG, calcarine gyri, parahippocampal gyri, posterior regions, cerebellum and precuneus. For brevity, only the six most predictive word categories across all of the models are displayed in Figure 9.

In Figure 9, a positive value in the map (red) indicates that a region contributed to the identification of high wellbeing participants. Conversely, a negative weight (blue) means that a region contributed to the identification of low wellbeing participants. The weight vector is essentially a weighted average of the support vectors, specifically the training examples that are most difficult to separate and define the decision boundary. The combination of all voxels as a whole is identified as a global spatial pattern by which the groups differ (the discriminating pattern).

Since the discrimination map is a spatial representation of the SVM weight, it does not directly quantify the information content of each region. Therefore, the discrimination map should not be interpreted as a standard statistical parametric map resulting from a test to find group differences. However, the spatial distribution of the weight vector does provide some information about the contribution of different areas to classification (Ecker et al., 2010).

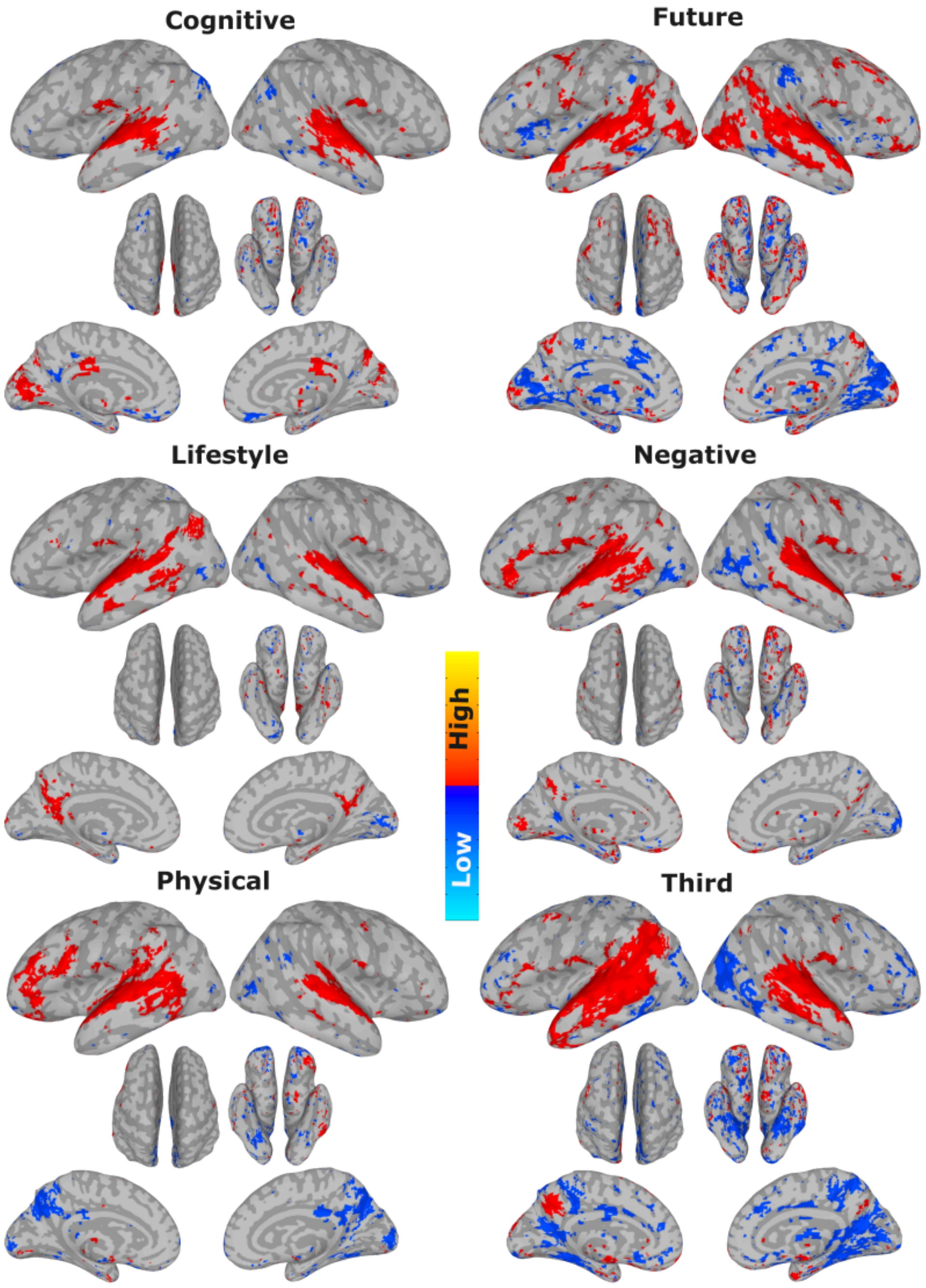


Figure 13. Discrimination map or SVM weight vector of high wellbeing versus low wellbeing for the six most predictive categories (as determined by their overall accuracy and F1 score). The colours represent the weight of each voxel in the classification function (the red scale represents positive weights and the blue scale represents negative weights).

Discussion

This study investigated the neural correlates of various linguistic categories and their relationship to wellbeing, utilising both univariate and multivariate approaches. Our findings reveal distinct patterns of brain activation associated with different word categories and demonstrate the potential of ML techniques to classify individuals based on their wellbeing status using neural responses to linguistic stimuli. Furthermore, the study gives a baseline proof of concept for the use of fMRI brain maps of language processing and comprehension being able to predict wellbeing states of participants. We also highlight the fact that low wellbeing participants can be differentiated at an above chance level from high wellbeing participants based on the way certain word categories are processed within the brain.

The subsequent research represents a significant step forward in integrating neurolinguistics with mental health research, offering a comprehensive analysis of the language-brain-wellbeing nexus. Through this work, we hope to pave the way for innovative therapeutic strategies that leverage the power of language to promote mental health and wellbeing. To our knowledge, this is the first study of its kind.

Neural Correlates of Linguistic Categories

Our univariate analyses revealed widespread activation patterns across multiple brain regions in response to different word categories. Notably, we observed consistent involvement of the temporal, occipital, and frontal lobes, as well as the precuneus, cuneus, AG, and insula. These findings align with previous research highlighting the distributed nature of language processing in the brain (Price, 2012), particularly with (Skipper, 2022)'s model, which posits that the brain processes language through a combination of sensory, motor, and cognitive systems, each activated depending on the context and type of linguistic input. The widespread activation observed across temporal, occipital, and parietal regions during the processing of different word categories supports this view.

While this supports theories that language is distributed across multiple neural circuits (Hickok & Poeppel, 2007; Skipper et al., 2017), alternative explanations must be considered. One possibility is that these activations reflect general semantic processing rather than a specific relationship with wellbeing. Previous studies have found that language processing co-activates regions involved in emotional and autobiographical memory processing (Binder et al., 2009), suggesting that our findings could be driven by the emotional valence of words rather than their wellbeing relevance. Future studies should employ finer-grained analyses to disentangle these possibilities.

Overall, our results showed that lifestyle and past tense words elicited the most widespread activations, engaging regions such as the MTG and the precuneus. These regions are consistent with those identified by Huth et al. (2016), who demonstrated the involvement of the temporal lobe in processing semantic information across various contexts. The temporal lobe's role in processing time-related language, especially past tense words, suggests that this region plays a crucial part in temporal cognition (Binder et al., 2009; M. H. Davis & Gaskell, 2009; Hagoort, 2014; Hickok & Poeppel, 2007). The significant bilateral activation suggests that these categories tap into cognitive processes related to self-reflection and personal experience, which are essential components of mental wellbeing (M. D. Lieberman et al., 2007).

Furthermore, the activation of the right MFG during the processing of past tense words further supports the idea that the frontal cortex plays a pivotal role in processing past, present and future thinking (Grodzinsky & Santi, 2008). These findings also corroborate previous studies suggesting that the frontal lobes are heavily involved in managing the executive aspects of language, including syntax, grammar, and the integration of contextual information (Friederici, 2011).

Moreover, the occipital regions, traditionally associated with visual processing, showed substantial involvement, particularly for the past tense and negative words. This could be interpreted as evidence for the visual-lexical pathway’s role in word recognition, a finding that resonates with prior studies on the fusiform and lingual gyri’s roles in visual word form processing (Dehaene et al., 2005; Price & Devlin, 2011). This also supports Skipper’s view that visual and contextual elements are crucial in language comprehension, particularly when stimuli are embedded in rich, multimodal environments like movies (Skipper, 2022).

Interestingly, negative words elicited a pattern of less activity when compared to controls in the left FG, which may suggest a suppression or decreased reliance on visual word form areas during the processing of emotionally charged or valence-specific linguistic information. This is in line with previous findings that suggest negative words tend to reduce activity in brain regions responsible for positive emotion and semantic association (Citron et al., 2013; Kensinger &

Schacter, 2006). This pattern also points to a suppression effect, suggesting that negative linguistic stimuli may reduce neural engagement in visual-semantic integration, a finding consistent with theories that depressive language patterns reduce broader cognitive functioning (Pennebaker & Lay, 2002; Rude et al., 2004).

Additionally, the role of the calcarine and lingual gyri, in processing physical and concrete words further supports this hypothesis that visual processing regions are involved in the semantic representation of concrete objects (Barsalou, 2008). Furthermore, the bilateral engagement of these regions for concrete and physical words underscores their significance in visual imagery and spatial cognition, reinforcing the aforementioned embodied cognition theory (Chapter 1) that posits a direct link between sensorimotor systems and language comprehension. This extensive involvement of the occipital lobe suggests that many of the word categories, particularly those related to temporality, engage visual processing areas, possibly indicating the need for mental imagery or scene reconstruction during language comprehension, though these regions were less affected by first person pronouns, suggesting a downregulation of visual imagery in self-referential contexts. This overtly highlights the complexity of processing social references at different levels of personhood and timespaces.

The observed activation of the precuneus and AG in response to lifestyle and social words provides additional evidence for the role of these regions in higher order cognitive processes, like self-referential processing and episodic memory (Cavanna & Trimble, 2006; Seghier, 2013). The significant engagement of the precuneus during lifestyle word processing may suggest that such words evoke personal and societal values, supporting the idea that this region integrates autobiographical information (P. Lieberman, 2002; Spreng et al., 2009). Additionally, the AG, which was activated for lifestyle and third-person words, is known for its role in TOM and perspective-taking, suggesting its involvement in processing language that requires the integration of external perspectives (Saxe & Kanwisher, 2003). Particularly, with third person references, it is inferred that mentalising is reduced during processing of such words when compared to the other groups of pronouns.

These regions are also part of the previously mentioned DMN (Chapter 1), which is involved in self-referential thinking and social cognition (Buckner et al., 2008). The engagement of the precuneus in the lifestyle and third-person word categories suggests that these types of words may evoke mental simulations of social interactions or autobiographical memories, processes that are central to the DMN’s function (Andrews-Hanna et al., 2010). The brain’s activation in response to these word categories suggests that promoting positive lifestyle choices and maintaining social connections, as reflected in linguistic expression, can activate brain areas that support healthy emotional regulation and self-awareness.

In addition, the reduced activity in the right cuneus for negation words could reflect the cognitive demands of processing negation, which requires inhibiting or suppressing affirmative meanings (Christensen, 2009). This is consistent with theories of cognitive control mechanisms involved in language processing, particularly when dealing with complex syntactic or semantic constructions such as negation. Thus, this region may be involved in error monitoring or conflict resolution during linguistic processing of negations.

One of the study’s more compelling findings, and which supports the initial hypotheses, is the distinction in neural responses based on emotional valence. Positive and past tense words elicited more extensive and positive neural responses than negative or future words, suggesting that the brain may engage more robustly with positive or familiar concepts compared to those conveying negativity or uncertainty. This asymmetry in activation, particularly in regions like the MTG and fusiform gyrus, could reflect underlying cognitive biases where the brain preferentially processes information that is familiar or emotionally neutral (Sharot et al., 2011).

On the other hand, first-person and future words, while still showing neural activity, elicited fewer regions of activation, which was contrary to the original hypotheses. This observation may indicate that words associated with personal pronouns and future-oriented contexts require less complex neural processing, possibly due to the inherently abstract or less emotionally charged nature of these categories (Saxe & Baron-Cohen, 2006), as has been suggested in prior research on time perception and self-referential processing (D’Argembeau et al., 2008). Skipper’s emphasis on the context-driven nature of neural activation may also help explain why future and first-person words activate fewer regions compared to more semantically rich categories like past tense and lifestyle words (Skipper et al., 2017). Skipper’s framework suggests that brain regions dynamically shift their roles depending on context, often suppressing areas to minimise cognitive load during emotionally taxing language processing (Skipper, 2014).

This self-referential processing is particularly relevant in mental health contexts, where individuals may ruminate on personal experiences or emotions. The increased activation of the PFC for first-person pronouns suggests that these words engage neural circuits related to self-awareness and introspection, which could explain why they are often associated with mental health disorders such as depression (Brockmeyer et al., 2015). The reduced activation in these regions for first-person pronouns may reflect the brain's efforts to disengage from excessive self-focus, which can be detrimental to mental well-being (Pennebaker & Lay, 2002).

The insula's reduced activation for future and positive words is also noteworthy, as the insula is often implicated in interoception and emotional awareness (Craig, 2014) and supports the initial hypotheses. This suggests that the processing of emotionally positive words may involve less engagement of affective networks, potentially due to their routine or familiar nature, compared to emotionally negative words that elicit more significant neural responses. This also suggests that these word categories may engage regions associated with emotional regulation and the integration of bodily states with cognitive processes.

The distinct patterns of activation observed in response to word categories with emotional valence lend some support to affective theories of language processing, which suggest that emotionally charged words engage additional neural networks related to emotion regulation and cognitive control (Kensinger, 2009).

Ultimately, our findings suggest that the neural correlates of language are not static but are influenced by the nature of the stimulus and the context in which it is presented. Skipper's argument that real-world language processing involves numerous brain networks is echoed here (Skipper et al., 2017).

Machine Learning Classification of Well-being

Our multivariate analyses using various ML models demonstrated the feasibility of classifying individuals' wellbeing status based on their neural responses to different word categories. The high accuracy achieved by these models, particularly the SVM and CNN, suggests that neural activation patterns in response to linguistic stimuli contain valuable information about an individual's psychological state.

The SVM model's superior performance in several categories (e.g., perfect accuracy for lifestyle, physical and third person words) indicates that these linguistic categories may be particularly informative for wellbeing classification. However, the SVM's struggle with recall in certain categories (e.g., drive and first person words) highlights the importance of considering multiple performance metrics when evaluating classification models. This also highlights the challenges of differentiating more abstract or emotionally neutral words, which may elicit less pronounced neural activations (Mitchell et al., 2008).

In sum, our use of ML models to predict wellbeing based on linguistic categories offers promising applications for mental health diagnostics. The success of the models, particularly SVM, in accurately categorising lifestyle, physical, and social words based on neural activation patterns demonstrates the potential for developing predictive models of mental well-being. This supports the idea that language use and the corresponding neural responses can serve as biomarkers for mental health, as proposed by recent research that merges language processing and fMRI data to predict psychological states (Bzdok & Ioannidis, 2019).

Implications and Future Directions

The results of this study contribute to a growing body of research on the neural correlates of language processing, emphasising the role of temporal, social, and emotional aspects of words in shaping neural activity. The distinct patterns of activation across different word categories reveal not only the complexity of language processing but also the differential engagement of brain regions based on emotional valence, temporal references, and personal pronouns. It also offers insights into how the brain processes language in ways that relate to mental health.

For example, the significant activation of the PFC in response to self-referential words could reflect increased rumination, a known risk factor for depression and anxiety (Palmer et al., 2014) Conversely, the activation of regions involved in social cognition (e.g., precuneus, AG) in response to lifestyle words may indicate a more adaptive processing style that promotes wellbeing through social connection and health behaviours.

Moreover, the findings on the suppression of neural activation in response to negative words (e.g., in the fusiform and cuneus) suggest that the brain may downregulate its response to emotionally negative stimuli, potentially as a protective mechanism. This supports theories of emotional regulation that propose individuals with better mental health are more effective at modulating their neural responses to negative stimuli (Kensinger, 2009).

Furthermore, these results align with the theories of Jeremy Skipper, who emphasises the distributed and dynamic nature of language processing in the brain. Skipper's model, which highlights how neural networks are contextually modulated during language comprehension, is supported by the diverse activation patterns observed across different word categories in this study (Skipper et al., 2017). The engagement of sensory, cognitive, and emotional networks for distinct linguistic categories mirrors Skipper's notion that language processing is not isolated to traditional language areas but is distributed across broader neural systems. This distributed activation further supports the idea that mental health is deeply connected to how we process and respond to language, both cognitively and emotionally.

By analysing neural responses to naturalistic stimuli, our findings suggest that different word categories engage distinct yet overlapping networks that are modulated by both linguistic and contextual factors. These results offer new insights into how the brain processes language in real-world settings, advancing our overall understanding of the neural underpinnings of mental wellbeing.

In addition, the success of machine learning models in classifying wellbeing based on neural responses to linguistic stimuli opens up new possibilities for developing objective, brain-based measures of psychological states. This could have significant implications for mental health assessment and monitoring.

For instance, cognitive-behavioural therapies (CBT) often focus on altering negative thought patterns by encouraging the use of more positive or neutral language. Insights into how specific words activate different brain regions can inform these therapeutic approaches, helping to tailor interventions to the individual needs of patients. Another example is linguistic analysis of patient speech or writing, which could provide further biomarkers for depression, anxiety, or other mental health disorders, offering a non-invasive and cost-effective way to assess mental health.

Therefore, the predictive models developed in this study could serve as objective, brain-based markers of mental wellbeing, complementing traditional self-report measures and clinical assessments. These models may aid the early detection of individuals at risk for mental health disorders and facilitate the monitoring of treatment response and progress.

And why is this so important? Because, by 2030, unipolar depressive disorders are thought to become the leading cause of disability in high-income countries. Yet in the UK, waiting times for access to primary mental health services could be up to 2 years. This is alarming as it suggests that existing procedures are inadequate, thus novel methods, as described, are needed to diagnose and treat these treatment resistant patients (Edbrooke-Childs & Deighton, 2020).

While the aforementioned talking therapies are primarily language-driven, it is important to acknowledge the broader factors that contribute to their efficacy. Beyond verbal communication, therapeutic outcomes are influenced by nonverbal elements such as tone, physicality, eye contact, silence, confidentiality, and the development of a therapeutic alliance through consistency, boundaries, and session structuring. For instance, a study by Ramseyer and Tschacher (2011) demonstrated that non-verbal synchrony between therapist and client is associated with better therapeutic outcomes and alliance. This synchrony includes factors such as body movement, posture, and facial expressions.

Cultural differences, socioeconomic context, and environmental factors also shape therapeutic engagement and effectiveness. A meta-analysis by Griner and Smith (2006) found that culturally adapted interventions were more effective than traditional approaches, highlighting the importance of cultural competence in therapy.

While language remains a primary medium for cognitive restructuring, emotional expression, and narrative reconstruction in talking therapies, these additional elements underscore the complex, multimodal nature of the therapeutic process. Moreover, while these factors undoubtedly influence the therapeutic relationship, they are often established and maintained through verbal communication. Therefore, language serves as an overarching medium that enables the effective utilisation of both spoken and unspoken elements in talking therapies. Future research should explore how these nonverbal components interact with linguistic processing in therapeutic settings to be able to draw any definitive conclusions.

Future research should also explore the connectivity between regions to further understand the interplay between language, emotion, and mental health. Additionally, by examining individual differences in neural responses to language, we may uncover new biomarkers for mental health outcomes, which could inform therapeutic interventions aimed at enhancing wellbeing through language-based strategies.

The NNDb is also continually evolving, with plans to expand its collection of movie stimuli and enrich the available annotations, as demonstrated in this thesis. This expansion will enhance its utility for investigating a broader range of cognitive and affective processes under naturalistic conditions. Future updates aim to further refine the dataset's usability, making it an invaluable resource for cutting-edge brain research. This has already become the case in the UNITy study (Chapter 4).

Limitations

One limitation of the current study is the use of a voxel-wise t-test approach, which may be sensitive to multiple comparison issues despite efforts to correct. Further analyses using more robust methods, such as MVPA or connectivity-based approaches, could provide additional insights into the neural networks underpinning language processing. Additionally, while our sample size was adequate for the analyses conducted, larger samples would allow for more robust and generalisable findings, particularly for the ML analyses, and there is no longitudinal trajectory data here, though this aims to be remedied as recruitment occurs in the following chapter for the UNITy study (Chapter 4).

Another central limitation lies in the way well-being was defined and operationalised. The study relies on a specific metric from the NIH toolbox, which, although comprehensive, may not fully encompass the multifaceted nature of wellbeing. Wellbeing is inherently complex, integrating subjective, psychological, and social dimensions that may not be entirely captured by quantitative tools. This limitation may have influenced the depth and scope of neural correlations observed, potentially skewing the model's predictive capabilities. Future studies should consider incorporating a broader set of qualitative and longitudinal wellbeing measures for a richer, more nuanced understanding, which is another goal of the overall UNITy project described in Chapter 4.

While the analysis accounted for variations in word categories, the relative inability to disentangle within-individual versus between-individual differences remains a limitation. People have unique cognitive styles and emotional responses to language, which could affect neural processing differently. The current study's design may not sufficiently parse out these individual idiosyncrasies, which could lead to averaging effects that obscure significant findings. Implementing methods such as mixed-effects models could enhance the precision of future research.

Despite using naturalistic movie stimuli to better mimic real-world language exposure, movies represent a curated and context-specific source of language. The responses elicited may not fully generalise to everyday communication or spontaneous language use. Including more diverse, real-life conversation samples or interactive tasks could improve ecological validity and bridge the gap between controlled experimental conditions and true-life scenarios.

Conclusion

In summary, the activation of diverse and context-dependent regions across different word categories in our study lends strong support to Skipper’s theory that language processing is a highly distributed, multisensory, and contextually modulated phenomenon. These results extend his model by demonstrating the specific neural mechanisms involved in processing linguistic categories that relate to time, person, and social cognition, further enriching our understanding of how the brain integrates multiple systems to comprehend language.

The use of the NNDb allowed us to capture the richness and complexity of real-world language processing, leading to findings that reflect more ecologically valid neural activation patterns. By linking linguistic categories to wellbeing outcomes, this research highlights the potential for developing language-based therapeutic interventions aimed at enhancing mental health through targeted cognitive and emotional regulation strategies.

The involvement of brain regions associated with social cognition, emotion regulation, and self-referential processing underscores the importance of language in mental health and wellbeing. These findings contribute to the development of predictive models of wellbeing based on neural responses to linguistic stimuli and provide a foundation for future research exploring language-based interventions to improve mental health. Overall, these findings suggest that the words we choose not only reflect but also influence our mental states.

Chapter 4: UNITy Study (Understanding Neuroplasticity Induced by Tryptamines)

Overview

Psychedelics like DMT, psilocybin, and LSD have recently gained attention for their potential to act as novel therapeutics in the treatment of psychiatric disorders, particularly for conditions that are resistant to traditional treatment modalities, such as major depression and anxiety disorders. However, the underlying mechanisms responsible for these therapeutic outcomes remain poorly understood.

One hypothesis suggests that psychedelics promote enduring changes in brain function through alterations in functional connectivity and neuroplasticity. These changes may support the 'reset' of maladaptive neural circuits involved in cognition, emotion, and self-referential processing, which are typically implicated in mental health conditions.

The UNITy study described in this chapter aims to investigate the neuroplastic effects of DMT, a potent, classical serotonergic psychedelic, by examining changes in brain activity and structure before and after DMT administration. Building on the NNDb paradigm outlined in the previous chapter, this study involves participants watching a movie in an fMRI scanner before and after taking DMT, providing a unique opportunity to study the impact of psychedelics on brain function and wellbeing.

The project aims to collect, analyse, and interpret neuroimaging and psychological data from participants undergoing psychedelic experiences, particularly focusing on understanding how these substances can be integrated into therapeutic practices and their potential benefits in mental health treatments, as well as their reaction with the neurobiology of language, a main focus of this thesis.

Introduction

Recent clinical research with psychedelic drugs has reignited interest in the therapeutic potential of psychedelics for psychiatric disorders, particularly in treatment-resistant forms of common mental health disorders, like depression and anxiety (Vollenweider & Kometer, 2010). Among the most-studied compounds in this class of ‘psychedelics’ are tryptamines, such as psilocybin, LSD and DMT (dimethyltryptamine). While these substances are all known for their potent psychoactive effects, DMT a naturally occurring tryptamine found in various plant species and used in traditional Amazonian rituals, has drawn significant attention for the rapid pharmacokinetics of its isolated form and its ability to induce profound (yet rapidly resolving)alterations in consciousness (Barker, 2018; Strassman, 2000). However, beyond its acute psychoactive effects, research has increasingly focused on the potential neurobiological and therapeutic impacts of DMT, particularly its influence on neuroplasticity and cognitive function (de Vos et al., 2021).

Emerging studies have demonstrated that DMT may have unique therapeutic value for addressing behaviours associated with anxiety and depression, particularly in populations that are resistant to traditional treatments (Cameron & Olson, 2018). This is particularly relevant as these conditions often involve maladaptive cognitive and emotional processing that is difficult to modify with conventional pharmacotherapies. DMT, like other psychedelics, appears to facilitate a "reset" of neural circuits involved in emotion regulation, cognition, and self-referential thought by modulating brain plasticity (Carhart-Harris & Nutt, 2017). These findings align with broader research suggesting that psychedelics promote structural and functional plasticity, particularly through pathways involving 5-HT2A receptor activation and enhanced glutamatergic transmission (Ly et al., 2018). The promotion of neuroplasticity is thought to be one of the key mechanisms through which psychedelics exert their therapeutic effects, facilitating the reorganisation of neural networks that govern mood and cognition (Hibicke et al., 2020).

Furthermore, single exposures to psychedelics, including DMT, have been associated with long-lasting changes in gene expression and synaptic connectivity, contributing to prolonged cognitive and emotional benefits. For example, research has shown that psychedelics can induce epigenomic alterations, which may underpin the observed sustained improvements in mental health (de la Fuente Revenga et al., 2021). These epigenetic changes suggest that the therapeutic effects of psychedelics extend far beyond the immediate psychoactive experience, with potential implications for the treatment of psychiatric disorders.

Functional imaging studies on DMT and other psychedelics have demonstrated changes in resting-state functional connectivity (RSFC), particularly in networks like the default mode network (DMN). The DMN is central to self-referential processing and is often hyperactive in conditions such as depression. Psychedelics have been shown to reduce DMN connectivity, correlating with the experience of ego dissolution and increased cognitive flexibility (Carhart-Harris et al., 2014; Palhano-Fontes et al., 2015). Such modulation of the DMN aligns with broader psychedelic research, which consistently reports that reduced DMN connectivity facilitates therapeutic effects by allowing for cognitive and emotional "resets" (Carhart-Harris & Nutt, 2017).

Furthermore, EEG studies have reported decreases in alpha oscillations and increases in global synchrony, indicating a shift in brain wave activity that supports enhanced cognitive and emotional flexibility (Timmermann et al., 2019). These EEG findings, combined with RSFC data, suggest that DMT and other psychedelics promote neuroplasticity and modify functional brain dynamics, potentially underpinning their therapeutic benefits.

Building on these findings, this chapter focuses on investigating the brain changes induced by DMT and their relationship to shifts in cognition, behaviour, language, and overall wellbeing. The fast-acting nature of DMT makes it an ideal candidate for studying acute neural and behavioural changes, particularly in the context of ASCs. By employing advanced neuroimaging techniques such as fMRI, this project aims to map the brain regions and networks affected by DMT, with a focus on language-related neural circuits and self-referential processing. Prior research has identified the DMN as a key area of interest, given its role in self-awareness and the fact that psychedelics consistently reduce DMN activity, correlating with the subjective experiences of ego dissolution and altered consciousness (Palhano-Fontes et al., 2015).

The integration of neuroimaging, linguistic analysis, and predictive modelling represents a novel approach to understanding the therapeutic potential of psychedelics. By combining these methodologies, this study seeks to bridge the gap between the subjective phenomenology of psychedelic experiences and objective, measurable brain changes. Moreover, this research may offer new perspectives on how psychedelics can be leveraged to promote psychological wellbeing by enhancing both neuroplasticity and linguistic flexibility, key factors implicated in resilience against psychiatric disorders.

Using the already trained predictive model developed in the previous chapter, which leveraged language-based neural activity to predict wellbeing, this study will apply a similar approach to the neuroimaging data collected from participants before and one week after an acute dose of DMT. The model will be used to assess whether brain changes induced by DMT correlate with improvements in mental health and cognitive flexibility. By doing so, this study aims to provide further insight into how psychedelic-induced neuroplasticity affects wellbeing, and whether these effects can be quantified through neuroimaging and predictive modelling (R. L. Carhart-Harris & Nutt, 2017; Savalia et al., 2021). Ultimately, the goal is to deepen our understanding of the therapeutic mechanisms of psychedelics, particularly in relation to their effects on brain plasticity and wellbeing, and to contribute to the growing body of research on their clinical applications.

This research is particularly timely, as the demand for innovative treatments for psychiatric disorders continues to grow, and psychedelics are emerging as a promising avenue for intervention (de Vos et al., 2021).

Research Objectives

The primary overall objectives of the UNITy project are:

- To observe and document brain activity and connectivity during and after the administration of DMT using fMRI.
- To compare these changes with baseline brain activity during naturalistic conditions, such as watching movies.
- To investigate how DMT affects the functional integration between language processing regions and other brain networks.
- To assess whether DMT-induced changes in network organisation persist beyond the acute phase.
- To investigate whether DMT-induced changes in language-related brain networks correlate with alterations in self-referential processing and emotional regulation.
- To track long-term effects on mood, behaviour, and mental health through continuous monitoring and follow-up assessments.
- To investigate whether specific patterns of language-related brain activity could serve as biomarkers for DMT's therapeutic effects.

Ultimately, the project seeks to understand both the immediate and lasting impacts of DMT on brain networks involved in language and sensory processing. These objectives are designed to bridge the gap between DMT's known neurobiological effects and its potential therapeutic applications.

Hypotheses

In this chapter specifically, we hypothesise that DMT administration will be associated with enduring changes in brain activity patterns during language processing, as measured one week post-administration during movie viewing. Specifically, we predict:

- Brain activity patterns during movie viewing will differ between pre- and post-DMT sessions in language-related networks (supporting findings from the meta-analyses in Chapter 2).
- We will observe differences in neural responses to specific word categories between pre- and post-DMT sessions:
    - Reduced activity in response to first-person pronouns in regions previously associated with self-referential processing.
    - Enhanced activity in response to drive-related words in regions associated with motivation and goal-directed behaviour.
    - Decreased activity in response to negative words in emotion-processing regions.
    - Increased activity in response to social-related words in regions involved in social cognition.
- The patterns of neural activity observed during word processing in the post-DMT session will show associations with participants' reported wellbeing scores, as assessed by the SVM model.

Note that all neural measurements are conducted during sober movie viewing (pre-DMT administration and one week post-DMT), not during acute DMT effects. This design allows us to examine potential lasting changes in language processing following DMT exposure, rather than acute drug effects.

Data Acquisition

Participants

Participants in the UNITy project include healthy individuals as well as individuals that score high on the AUDIT (Alcohol Use Disorders Identification Test) scale. Recruitment is carefully managed to ensure diverse demographic representation, covering various ages, genders, and backgrounds. All participants undergo thorough screening to assess their eligibility and suitability for the study. This includes comprehensive assessments of their physical and mental health, as well as their medical history. The data forms part of the larger UNITy study.

Recruitment faced significant delays due to the COVID-19 pandemic and logistical challenges, leading to a current pilot sample size of four participants (aged 21–45) at the time of this thesis (recruitment is ongoing). Inclusion criteria required participants to have no history of severe psychiatric or neurological conditions and no contraindications for psychedelic substances. Each participant provided informed consent before participation. Although the overall UNITy study is now focusing on AUD, all participants in this thesis came from the normative sample, therefore the other parts will not be reported here.

Procedures

After being screened for eligibility, participants visit the lab on three separate occasions to complete a battery of tests and questionnaires. However, at the time of writing this thesis, the only readily available and synthesised data came from the WEMWBS questionnaire, and, so, the other tests and questionnaires are not discussed further or are of relevance to this thesis.

Visit 1

In visit 1, participants give full and informed consent before undergoing a more extensive review of their eligibility, which includes neuropsychiatric screening, cardiorespiratory assessment and a breath/urine alcohol and drug screen. Also included are measurements of height, weight, pulse and systolic and diastolic supine blood pressure. Alcohol content is screened using a breath test with the Lion 500 Alcometer and recreational drugs, namely cannabinoids, amphetamines, benzodiazepines, cocaine and opiates, using mid-stream urine collected in a sterile container. A positive result in either test will result in exclusion from the study. Also on this day participants complete a battery of questionnaires and an alcohol verbal fluency task, though these will not be discussed in depth as they are not relevant to the scope of this thesis.

After completing the questionnaires and task, participants are escorted to the scanning suite for functional and anatomical fMRI. The scanning procedure follows that of Chapter 3, though with only four movies rather than 10, and also introducing eye movement, heart and pulmonary activity tracking. Like Chapter 3, the scan is split into three runs, allowing the participant to have an adequate break.

Once the movie is complete, a high resolution anatomical scan is acquired. Participants are then briefed for visit 2 before leaving.

Visit 2

On visit 2, participants review their consent, and, as described in Chapter 3, the scanning suite is set up for their comfort and, as described in Visit 1, a full eligibility review is redone.

Afterward, the interviewer openly discusses the commonly reported subjective effects of DMT and also offers advice for navigating the subjective experiences based on insights from previous studies and the Acceptance and Commitment therapy framework (Timmermann et al., 2020). Participants then receive another battery of questionnaires to complete before cannulation begins.

With an indwelling catheter in their non-dominant forearm, hand or ankle, depending upon accessibility of veins, a medical assistant or trained member of the experimental team will perform the cannulation. These are performed according to full aseptic non-touch techniques. The infusion is controlled by two Alaris PK syringe drivers, set to bolus/infusion speeds for the relevant dose as determined by the pharmacokinetic model developed by Small Pharma (Good et al 2023, James et al 2024). Following this, the cannula is removed, and the participant is continually monitored throughout the process, with heart rate and respiration measures. In case of adverse reactions, the medical assistant is able to terminate the infusion.

The procedure described in Visit 1 is repeated as participants complete a 20 minute eyes-closed resting state scan before completing an alcohol memory reactivation paradigm outside of the scanner. As above, this is not relevant to the scope of the thesis, and so will not be discussed.

The fMRI operator signals whether they are ready to begin DMT or placebo infusion via an intercom system. The infusion lasts for 20 minutes during which a second resting state fMRI scan is collected.

Following DMT, participants are able to remain in the scanner until they are comfortable enough to leave. After this, the study clinician confirms that participants are no longer experiencing any residual subjective effects of DMT administration. This is followed by participants taking part in a qualitative semi-structured interview that gives them the opportunity to vocalise and discuss their experience. The second experimenter also creates a timeline of the experience, which is verified by the participant. As this data is not use within the thesis, it will not be discussed.

There is also Visit 3, though, as above, the data is not used in the thesis (this session was used to fill out more questionnaires), and, so, it is not discussed further.

Stimuli

Due to the nature of the study and to minimise order effects, the movies presented during the fMRI sessions were counterbalanced across participants. Counterbalancing ensured that participants viewed different combinations of the movies across sessions, with two movies per session. Participants initially watched Withnail and I (1987, 107 minutes) paired with Lost in Translation (2003, 102 minutes), but due to high familiarity with Lost in Translation among participants, it has since been replaced by Risky Business (1983, 99 minutes). The Big Lebowski (1998, 117 minutes) was similarly replaced with The Trip (2010, 112 minutes).

However, the main pairing at the time of this thesis was Withnail and I (1987, Comedy/Drama) and Lost in Translation, alongside Cocktail (1988, Comedy/Drama, 104 minutes). Movies were chosen due to their inclusion of alcohol-related themes, integral to the AUD component of the study. The number of alcohol-related terms in each movie is detailed below:

- Withnail and I: 351 alcohol-related words
- Lost in Translation: 118 alcohol-related words
- Risky Business: 203 alcohol-related words
- The Trip: 408 alcohol-related words
- Cocktail: 264 alcohol-related words
- The Big Lebowski: 394 alcohol-related words

Participants were shown two movies, one in session one pre DMT administration, and again in session 3 post DMT administration.

Since the participant scans of the healthy arm available at the time of this thesis, only watched a combination of Withnail and I and Lost in Translation or Lost in Translation and Cocktail, these were the only transcripts that I annotated (using the same procedure as Chapter 3). This resulted in, across all movies, 1293 cognitive words, 356 drive words, 891 first person pronouns, 289 future tense words, 412 lifestyle related words, 569 negations, 184 negative words, 489 past tense words, 1590 perception words, 415 physical words, 353 positive words, 530 present tense words, 426 second person pronouns, 787 social related words and 365 third person pronouns. A full breakdown is displayed in Table S4. There are less words in Lost Translation due to the movie having the shortest script and lacking in overall language use.

Drug administration

DMT is administered through a controlled intravenous infusion. This method ensures that the drug bypasses metabolic enzymes that would otherwise degrade it, allowing for a consistent and intense psychedelic experience. Participants received a single administration of DMT via intravenous infusion. The dose was calibrated to induce a psychoactive experience (25-27.5 mg). During the infusion, which lasts about 10 minutes, participants are continuously monitored, with medical personnel present to ensure safety.

Prior to the administration, participants engaged in movie watching fMRI protocol (as previously described in Chapter 3), and post-DMT neuroimaging data were acquired approximately 30 minutes after peak psychedelic effects. Administration will follow a double-blind procedure, with a placebo control, though, as mentioned, due to time constraints, this was not feasible for the scope of this thesis, therefore only pre/post DMT scans are reported here.

Acquisition

Similar to Chapter 3, an echo-planar imaging (EPI) sequence with a multiband acceleration factor of four is used. However, the TR is increased to 1.5 seconds and a 3T Siemens Prisma scanner with a 30 channel head coil (Siemens Healthcare, Erlangen, Germany) is used throughout (TE = 35.20 ms, flip angle of 60°, 72 interleaved slices), alongside heart rate, respiration and eye gaze position measurements. High-resolution fMRI data is collected during both pre- and post-DMT sessions.

Preprocessing

Preprocessing was also conducted on this data following much of Chapter 3’s procedure, though the script differed slightly. Below the stages are touched upon, with differences being described more in depth.

Anatomical dataset is warped non-linearly with SSWarper. Then recon-all to make it fit the freesurfer space. Recon-all again to align to the freesurfer MNI space. Then MNI to SUMA and SUMA MNI. So some of these files could be used as BIDS, if required at a later stage in the project.

Step 5 using afni_proc.py to blur and censor the functional dataset of each of the three runs separately. Like Chapter 3, all runs were first despiked, volume registered and time shifted (though in this case the first 8 TRs were dropped from the first run, 16 TRs from run 2 and also 16 TRs from run 3). Similarly, a mask was applied and they were aligned to the MNI space.

The fMRI scans collected during the DMT sessions will, in future, be compared to scans taken while participants watch movies in a sober state. This comparison can help to elucidate how DMT alters sensory processing and brain network organisation in naturalistic, real-world stimuli.

Movies were shown in 2 visits per participant, with each session lasting approximately two hours, including both the movie-watching period and a baseline scan, but not accounting for the interview and questionnaire phase.

Questionnaires

Although a variety of questionnaires are to be administered when the UNITy project starts recruiting, I only had access to the Warwick Edinburgh Well Being Scale (WEMWBs) (Tennant et al. 2007). At the time of writing, and with the participants included in the thesis, this 14-item test measured on a Likert scale was the only questionnaire fully answered in both pre and post sessions. As reported, a score of ≤40 could indicate depression, or low wellbeing. Therefore, I defined low wellbeing as scoring ≤40 and high wellbeing as anything above this.

Long-term Follow-Up Using Mobile Applications

Participants' experiences and mental states are continuously monitored for up to one year through an experience sampling mobile app. This long-term data collection helps in assessing how DMT-induced changes in brain function relate to sustained changes in mood, cognition, and wellbeing.

Data Analysis Techniques

GLM Analysis

A GLM was applied using AFNI's 3dDeconvolve software, as described in the previous chapter. Separate GLMs were conducted for the two sessions (session 1 and session 3) individually. Each session's brain data was regressed onto the word categories to capture the BOLD signal related to specific linguistic elements in the movies.

Contrast Analysis

After estimating the GLMs for each session, a subtraction-based contrast analysis compared brain activity related to wellbeing words across the two sessions. The difference in activity between pre- and post-DMT sessions allowed us to identify voxels exhibiting significant changes in response to specific word categories.

The resulting contrast images were then input into the previously described SVM model for classification analysis, focusing on identifying discriminating voxels predictive of changes in wellbeing states.

Statistical Analysis

Statistical analysis, as previously described, of the GLM contrasts was conducted using AFNI's 3dttest++. A paired ttest was conducted using the words and matched controls. A correction for multiple comparisons was applied using an FDR threshold of $p < .01$ with a minimum cluster extent of 40 voxels. Due to the small sample size, however, there were only three degrees of freedom in this preliminary analysis.

Questionnaire Measures

Predictive Model Application

The SVM model, developed in the previous chapter and trained on language-related neural patterns from the NNDb dataset, was applied here, in this chapter, to the contrast maps (pre DMT vs post DMT) derived from the GLM analysis. This was due to the SVM's highest overall accuracy, and the ability to identify discriminating/diagnostic weights (Chapter 3). But since the dimensions of the studies differed, 3dResample was initially used to standardise the dimensions.

The primary goal is to predict post-DMT wellbeing scores, which are to be collected using various psychometric scales, though only one is described in the scope of the thesis. The discriminating voxels from the SVM model are hypothesised to correlate with shifts in wellbeing, emotional regulation, and cognitive flexibility, which could, in turn, lead to neuroplasticity.

Results

Due to the small sample size ($N = 4$) and the ongoing nature of the study, preliminary results should be interpreted with caution. Figure 10 illustrates the full set of results, highlighting significant clusters of brain activity changes between pre- and post-DMT sessions. These changes were distributed across multiple brain regions, including those related to self-referential processing, motor planning, and social cognition. Second person words were not robust enough to survive the thresholding.

As hypothesised, there was a decrease in activity associated with first-person words in brain regions linked to self-referential processing. Specifically, post-DMT, significant reductions in activity were observed in the left postcentral gyrus ($x = -52$, $y = -32$, $z = 52$, 959 voxels), and the right inferior parietal lobule ($x = 40$, $y = -52$, $z = 56$, 523 voxels).

Similarly, as predicted, the processing of drive-related words was associated with significant increases in activity in several regions post-DMT. The most prominent changes were observed in the right precentral gyrus (x = 64, y = 4, z = 36, 1629 voxels) and the left postcentral gyrus x = −60, y = −8, z = 48, 1132 voxels).

Consistent with the hypothesis that DMT reduces the emotional impact of negative stimuli, there was a decrease in activity in brain regions associated with processing negative words. The left supramarginal gyrus (x = −64, y = −24, z = 28, 183 voxels) and the right supramarginal gyrus x = 64, y = −32, z = 36, 161 voxels).

Another prediction was an increase in activity in regions associated with social cognition when participants processed social words post-DMT. The left supramarginal gyrus x = −64, y = −24, z = 28, 925 voxels) and the right MTG x = 48, y = −28, z = 0, 665 voxels).

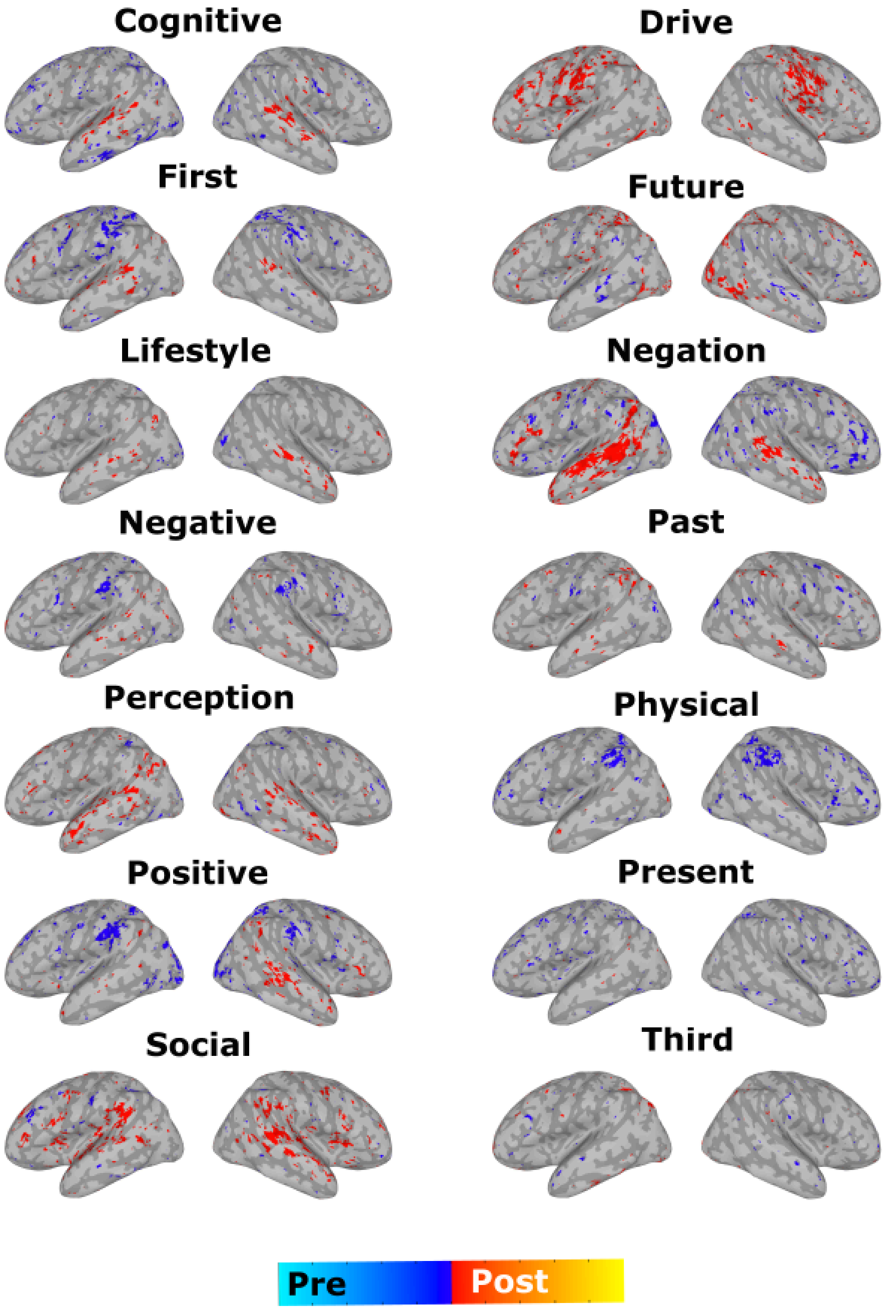


Figure 13. Group level ttest results of all of the word categories FDR corrected (*p* < .01), with a cluster extent threshold of 40 voxels. Hot colours (i.e. red) show areas of increased activity post DMT infusion while cold colours (i.e. blue) show areas of reduced activity post DMT infusion. Second person words did not survive statistical thresholding.

Predictive model performance

Since the questionnaire data has not yet been synthesised accordingly, a full evaluation of the model is not possible, and only preliminary supporting vector weights can be shown in this thesis, awaiting approval when the data becomes readily available. Still, the preliminary analyses show a predicted higher wellbeing class post DMT (>40 on the WEMWB) in almost all of the word categories when given the beta map of the contrast (described above) between the pre and post scans. Figure 11 shows the corresponding SVM vector weights.

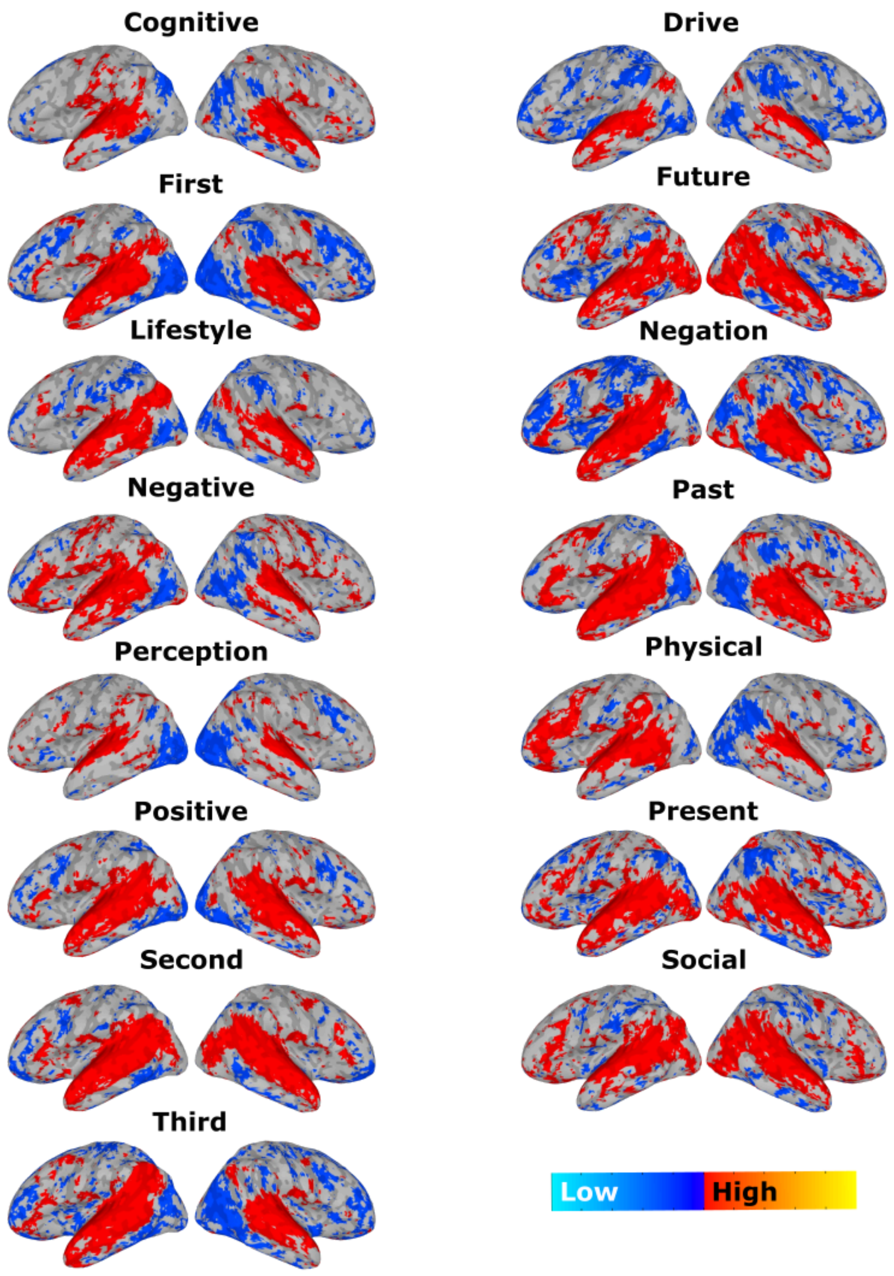


Figure 14. Discrimination map or SVM weight vector of high wellbeing versus low wellbeing for the fifteen word categories ($p < 0.05$, uncorrected). The colours represent the weight of each voxel in the classification function (the red scale represents positive weights and the blue scale represents negative weights).

Discussion

Summary

Overall, our findings indicate an engagement of distributed brain regions, including but extending beyond classical language areas, which suggests that different word categories are processed by distinct neural circuits. This differential engagement supports the idea that different types of wellbeing or mental health may be supported by distinct cognitive and linguistic processes.

Importantly, the results indicate that DMT affects brain regions beyond just the language-specific areas, implying that linguistic flexibility under psychedelics may be mediated by broader cognitive networks. These findings align with work which suggests that language processing in the real world often involves multimodal sensory integration (Huth et al., 2016).

The findings in some categories support initial hypotheses. For instance, the observed decrease in activity associated with first-person words in brain regions linked to self-referential processing is consistent with prior studies suggesting that DMT reduces self-referential thought by disrupting the DMN (Carhart-Harris et al., 2014). The specific reductions in the postcentral gyrus and inferior parietal lobule may indicate a diminished focus on the self, contributing to the experience of ego dissolution that is commonly reported during DMT experiences (Lebedev et al., 2015).

Similarly, the increase in activity associated with drive-related words post-DMT suggests an enhancement of intrinsic motivation and goal-directed behaviour, as reflected in the activation of the precentral and postcentral gyri, regions involved in motor planning and sensory processing (Tagliazucchi et al., 2014). This aligns with findings that psychedelics can increase cognitive and emotional flexibility, facilitating more adaptive behaviours (Carhart-Harris et al., 2017).

The reduction in activity in regions linked to processing negative words, such as the supramarginal gyrus, supports the hypothesis that DMT reduces the emotional impact of negative stimuli. This finding is consistent with evidence that psychedelics can modulate emotional regulation and decrease reactivity to negative stimuli, potentially contributing to their therapeutic effects in mood disorders (Mertens et al., 2020; Cameron & Olson, 2018).

Finally, the increased activity in brain regions associated with social cognition, such as the supramarginal gyrus and MTG, during the processing of social-related words post-DMT suggests an enhanced awareness of others. This could reflect the heightened sense of connectedness and empathy often reported during psychedelic experiences (Griffiths et al., 2006), reinforcing the potential of psychedelics to improve social functioning and interpersonal relationships (Palhano-Fontes et al., 2015).

Although, at present, the small sample size precludes any statistical significance testing within the predictive model, initial trends indicate that DMT-induced changes in neural activity are associated with positive shifts in wellbeing measures, particularly in brain regions implicated in language and emotional regulation.

Language and Emotional Processing Under Psychedelics

One of the unique aspects of the UNITy study is its focus on the interaction between psychedelics and language, a critical but underexplored area in psychedelic research. Language is not only a medium for communication but also a cognitive tool that shapes self-reflection, emotional processing, and social interactions (Dennett & Dennett, 1993). In this study, we used movie stimuli containing diverse linguistic content to examine how DMT influences the neural processing of language categories associated with wellbeing. Our results show that different linguistic categories—such as social, emotional, and self-referential words—engage distributed brain regions beyond classical language areas, suggesting that DMT may modulate a broader range of cognitive processes than previously thought.

Previous research suggests that psychedelics enhance cognitive flexibility and promote more fluid associations between linguistic and emotional content, potentially leading to therapeutic effects in conditions such as depression and anxiety (Carhart-Harris & Nutt, 2017). Our findings align with this, showing significant neural changes in regions involved in both language and emotional regulation, particularly in response to social-related words and pronouns. These changes suggest that DMT may facilitate shifts in emotional processing, contributing to improvements in mood and cognition observed in post-DMT assessments.

Additionally, this research builds on previous work that identified language-related neural patterns as significant predictors of psychological states (Tagliazucchi, 2022). The inclusion of movie stimuli allowed us to study language in a naturalistic context, offering a real-world perspective on how psychedelics influence language processing. This context-based approach revealed that DMT affects not only classical language areas (e.g., the STG) but also regions linked to emotional and social cognition, such as the inferior parietal lobule and supramarginal gyrus. These findings suggest that the therapeutic effects of psychedelics may extend to enhancing the flexibility of both linguistic and emotional networks, potentially offering new pathways for treating psychiatric disorders.

The results also underscore the importance of considering distributed brain regions in understanding how psychedelics influence cognitive and emotional processing. Different linguistic categories activated distinct networks, implying that DMT’s effects on mental health may be mediated by a wide array of cognitive processes. This distributed activation could explain why certain word categories are stronger predictors of positive mental health outcomes.

Predictive Modeling and Wellbeing Outcomes

The application of the SVM model in this study to predict wellbeing from neuroimaging data represents a novel and promising approach. By identifying discriminating voxels related to wellbeing, we demonstrated that changes in brain activity under DMT could be used to forecast individual mental health outcomes. Previous research has shown that psychedelics induce plasticity in brain circuits involved in mood regulation, such as the DMN and SN, leading to improvements in wellbeing (Savalia et al., 2021). The results from this study, though preliminary due to the small sample size and time constraints, support this hypothesis. The SVM model mostly predicted a higher wellbeing group based on the neuroimaging contrasts between pre- and post-DMT sessions, suggesting that brain activity changes associated with wellbeing words are meaningful predictors of mental health improvements.

Beyond predicting wellbeing, this approach provides valuable insights into the underlying mechanisms of DMT’s effects. By pinpointing specific brain regions involved in language, self-referential processing, and emotion regulation, the model reveals the networks likely driving these therapeutic outcomes. For instance, reductions in DMN activity may facilitate ego dissolution and emotional flexibility, while changes in the SN may enhance the processing of salient emotional stimuli. These findings indicate that DMT’s impact on these networks underlies its potential to improve mood and cognitive flexibility, contributing to its broader therapeutic effects.

This predictive modelling approach holds significant potential for personalised medicine, where predictive models based on neuroimaging data could be used to tailor psychedelic therapies to individual patients. As the demand for innovative mental health treatments grows, predictive models like the one used in this study may offer a way to optimise PAP for conditions such as depression, anxiety, and addiction, based on each patient's unique neural profile (Kočárová et al., 2021).

Neuroplasticity and Psychedelic-Induced Brain Changes

The neuroplastic effects of psychedelics, particularly tryptamines, have been increasingly recognised as central to their therapeutic potential (Ly et al., 2018). Psychedelics have been shown to promote synaptogenesis, dendritic spine growth, and functional brain connectivity, which are key mechanisms underlying their ability to induce long-lasting changes in cognitive and emotional processes (de la Fuente Revenga et al., 2021). The findings from this study, though preliminary, align with this body of literature, suggesting that DMT may reorganise brain networks involved in self-referential processing and emotional regulation as referenced by language processing.

DMT’s ability to modulate the DMN is particularly noteworthy. The DMN, which includes key regions such as the mPFC and PCC, is heavily involved in self-referential thought and the maintenance of the ego. Psychedelics have been shown to disrupt the functional integrity of this network, correlating with experiences of ego dissolution and altered states of consciousness (R. L. Carhart-Harris et al., 2014; R. L. Carhart-Harris & Friston, 2019). In this study, we observed significant changes in activity of regions in the DMN between the pre- and post-DMT sessions, particularly in response to emotionally and linguistically loaded stimuli from the movie-watching task. This finding reinforces the hypothesis that psychedelics induce a temporary disintegration of the DMN, facilitating a "reset" of maladaptive cognitive patterns (Tagliazucchi et al., 2014).

Methodological Challenges and Limitations

The primary limitation of this study is the small sample size (*N* = 4), which limits the generalisability of the findings and the statistical power of the analyses. The necessity to replace certain movies due to participant familiarity (e.g., replacing Lost in Translation with Risky Business) and to counterbalance the remaining films highlights the challenges inherent in studying complex real-world stimuli, such as movies, in neuroimaging paradigms. Lost in Translation is also very lacking in terms of language in comparison to the other movies. For instance, Lost in Translation only has around 5200 words overall in comparison with the almost 10000 in both Withnail and I and Cocktail.

Another main limitation in the study was that, in order to capture the effects of the DMT experience, the input was the beta values of the contrast between the pre DMT and post DMT scans, rather than just an input from one scan session, as was the case in the prior chapter. This added an extra layer of complexity to interpreting and comparing the data. An attempt was made in the results, though this is only suggestive. Still, this discrepancy means that the model trained on NNDb data may not accurately classify or predict outcomes in the UNITy data, as it was not optimised to interpret contrast-based data. Additionally, since most word categories gave a high wellbeing rating following DMT administration, it was also hard to gauge the true accuracy of the classification in this case. This uniformity, combined with differences in dataset structure, raises concerns about the robustness of the classification model when applied to the UNITy dataset, as it was trained on data with a different conceptual basis and structure. These factors suggest caution in interpreting the results, as model predictions may be influenced by these inconsistencies. As stated, future studies should aim to look at larger, more varied data in order to make any definitive conclusions.

In addition, the differential number of words per category could influence the prediction accuracy for each category. Therefore, future work should explore whether there is a correlation between the number of words in a category and the prediction score, although initial analysis does suggest that this is unlikely. The potential influence of correlated visual information from the movies on brain activity should also be considered. However, this is not necessarily a weakness, as it reflects how words are processed in real-world contexts, as supported by previous research (Huth et al., 2016).

Technically, a notable limitation is the difference in scanner magnetic strength between datasets; the NNDb data was acquired with a 1.5T fMRI scanner, while the UNITy study data uses a 3T scanner. Variations in field strength can lead to differences in signal-to-noise ratios, spatial resolution, and contrast sensitivity, potentially affecting the consistency and comparability of neural activity data across datasets, though all data in this chapter was resampled to the best of our ability.

Another limitation is that every word category seemed to predict wellbeing, raising the possibility that general linguistic features, rather than wellbeing-specific terms, drive the predictions. Thus, future studies should include more control words, i.e. random, unmatched words, to assess the specificity of the predictions. Lastly, another limitation is the restriction to GLM analysis in this phase of the project. While future work in the lab will involve more sophisticated connectivity analyses, the current study is confined to a GLM approach due to time and resource constraints. However, the use of the SVM model provides a valuable step toward predictive modelling in this context, allowing for the identification of discriminating neural voxels related to wellbeing.

The findings remain suggestive, pointing toward promising directions for future work. Addressing these limitations in subsequent studies, particularly through standardising scanner types with more data, could help enhance model accuracy and reliability in predicting wellbeing outcomes based on psychedelic-induced neural changes.

Applicability of the Predictive Model to DMT Data

Given that the predictive model trained in Chapter 3 was applied to the DMT dataset, it is necessary to assess its applicability in this context. The primary challenge in applying this model lies in the temporal differences between the training and target datasets. The original model was trained using fMRI data collected acutely, whereas the current study analysed pre- and post-dose imaging. This difference in methodology raises the question of whether the predictive features identified in the previous chapter remain valid in a post-hoc setting. While the model showed reasonable predictive accuracy, the acute effects of psychedelics on brain activity can differ significantly from the longer-term neuroplastic changes that may occur following psychedelic use. This temporal mismatch could potentially limit the model's sensitivity to detect changes in wellbeing related to DMT-induced neuroplasticity, highlighting the need for cautious interpretation of our findings. Nevertheless, given the exploratory nature of this pilot study, we believe that the application of this model provides valuable insights into the potential effects of DMT on wellbeing.

In future research, we aim to develop models specifically tailored to pre- and post-dose imaging data, potentially improving the accuracy and applicability of our predictions. Additionally, we will explore alternative modelling approaches to further enhance our understanding of the complex relationship between DMT and wellbeing.

Clinical and Therapeutic Implications

Despite these limitations, the current study's focus on the relationship between DMT administration and wellbeing is particularly timely, as the demand for innovative treatments for mental health disorders continues to rise (Nyugen, 2022). Therefore, the findings from the UNITy study have important implications for the clinical application of psychedelics in mental health treatments. Psychedelics like DMT have shown promise in treating a variety of psychiatric disorders by promoting neuroplasticity and resetting dysfunctional brain circuits (Hibicke et al., 2020). This study's focus on the interaction between language and wellbeing highlights the potential for using psychedelics to enhance cognitive and emotional flexibility, which are key targets in the treatment of depression, anxiety, and addiction (de Vos et al., 2021; Hibicke et al., 2020).

Moreover, the decision to include alcohol-related movies in the fMRI paradigm reflects the potential for using psychedelics to treat AUD. These findings are consistent with previous research showing that psychedelics like psilocybin and DMT can reduce cravings and promote abstinence in individuals with substance use disorders (Bogenschutz & Johnson, 2016). As more data from the UNITy project are collected, the therapeutic potential of DMT for treating AUD and other psychiatric conditions will become clearer.

The application of GLMs and subsequent SVM analysis in this study aimed to assess how DMT-induced changes in language-related brain networks correlate with shifts in wellbeing. The results showed that regions typically associated with language processing, such as the left IFG (Broca’s area) and the PSTG (Wernicke’s area), exhibited altered activity following DMT administration. Although only preliminary and short-term data, these changes were linked to participants' initial subjective wellbeing scores, indicating that DMT’s effects on the brain's language networks may play a crucial role in its therapeutic potential. These findings are also in agreement with the meta-analysis in Chapter 2, which suggests that language-related regions may mediate the subjective effects of psychedelics.

Additionally, this is consistent with broader research suggesting that language flexibility, including the ability to reconceptualise and reframe internal narratives, is a key factor in resilience against psychiatric disorders (Deveci et al. 2024). By enhancing linguistic and cognitive flexibility, DMT may enable individuals to break free from rigid, maladaptive thought patterns, contributing to long-term psychological healing (Doss et al. 2021; Davis et al. 2020)

This could be especially useful in those with AUD, which is the next stage of the UNITy study, as a whole. Since we chose movies with a high amount of alcohol-related terms, the neural response to these alcohol-related terms under the influence of DMT could provide future insights into how psychedelics might modulate reward-related brain networks, which are often implicated in addiction (Griffiths et al., 2006).

Significance and Future Directions

The UNITy Project is poised to provide significant insights into the effects of DMT on the human brain and its potential therapeutic benefits. Expected future outcomes include:

- **Detailed maps of brain network changes**: Understanding how DMT alters the organisation and functioning of brain networks involved in complex processes like language and memory.
- **Behavioural correlations**: Linking changes in brain activity during DMT exposure to subsequent modifications in mood, behaviour, and overall well-being.

Moreover, the project represents a pioneering endeavour in comprehending the neuroplastic effects of tryptamines. By elucidating the mechanisms through which tryptamines impact neuroplasticity, the project contributes to the expanding knowledge on the therapeutic potential of psychedelics in psychiatric disorders. As the first large-scale study to examine the neural impact of DMT in such depth, UNITy stands at the forefront of psychedelic research.

Conclusion

In conclusion, the UNITy study provides a foundational step toward understanding how DMT-induced neuroplasticity can be harnessed to predict wellbeing outcomes. By focusing on brain activity changes during movie-watching tasks, this study offers novel insights into how psychedelics influence the brain's language and emotional networks. While the small sample size and reliance on GLM analysis present limitations, the preliminary findings suggest that psychedelic-induced neuroplasticity holds significant potential for enhancing mental health.

Ultimately, the UNITy project contributes to the growing field of psychedelic science by offering new perspectives on the therapeutic mechanisms of DMT and its impact on brain plasticity, wellbeing, and language processing. With continued research and development, psychedelics may offer a transformative approach to treating psychiatric disorders, providing hope for those who have not found relief through conventional treatments.

Chapter 5: Discussion

Overview

By delving into the neurobiology of language, examining the neurobiological impacts of psychedelics, and investigating how these elements converge to influence conscious experience and mental health, this research provides novel insights into the profound and multifaceted connections within the human brain. This discussion synthesises the findings from the preceding chapters and positions them within the broader context of existing literature, highlighting the implications for future research and potential clinical applications.

Language Processing: Beyond Static Regions

Language, as a tool for communication and self-expression, is not merely a superficial layer of cognition but deeply entwined with the very fabric of our subjective experience. The neurobiological underpinnings of language, as elucidated in the introduction, reveal a complex network of brain regions involved in language processing, extending beyond the classical model of Broca's and Wernicke's areas (Calabria et al., 2018; Friederici, 2012). Neuroimaging studies, for example, have shown that the basal ganglia and the cerebellum also play crucial roles in language modulation, particularly in timing and motor aspects of speech production. The Dual Stream Model and subsequent distributed network theories further emphasise the widespread neural architecture supporting language function (Hickok & Poeppel, 2004). The study of ASCs and language disorders i.e. aphasia, specific language impairment, and dyslexia have provided valuable evidence for these theories (Bishop et al., 2014). Therefore, this thesis aligns with the distributed network theory, emphasising that language-related brain activity is not confined to classic regions but involves a broader, interconnected network that supports complex cognitive functions (Mesulam, 1990).

A key hypothesis in this thesis was that language processing is not confined to traditionally defined ‘language regions’ such as Broca's and Wernicke's areas but involves multiple networks of brain regions for semantics cooperating with networks for cognitive and emotional processes. Using data from the NNDb in Chapter 2, the empirical analysis of wellbeing word categories (including cognitive, positive, negative, and social terms) demonstrated that language processing is dynamically integrated with networks responsible for self-referential thought, emotional regulation, and perceptual processing. These findings align with the broader HOLISTIC theory proposed by Jeremy Skipper, which argues that language comprehension is a multisensory and context-dependent process, involving a large array of neural networks that extend far beyond the static "language centres" (Skipper et al., 2017).

For instance, when participants processed cognitive words, activity was observed not only in regions traditionally associated with executive function, such as the dlPFC, but also in regions involved in emotional processing, such as the insula. This suggests that language, particularly words related to abstract thought, recruits networks involved in both cognitive control and emotional regulation. Similarly, social and second-person words activated areas like the supramarginal gyrus and the MTG, regions known for their role in perspective-taking and social cognition (Schurz et al., 2014).

Similarly, emotion-related words—both positive and negative—engaged the limbic system and ACC, regions typically involved in emotional processing and emotional regulation (I. J. Roseman, 2018). This underscores the emotion-cognition integration that is central to wellbeing, with language playing a key role in how we construct and process emotional experiences. The findings suggest that the neural correlates of wellbeing involve a complex interaction between linguistic meaning, emotional regulation, and self-referential thought, further demonstrating that language is not isolated to static brain regions but instead emerges from distributed neural systems.

These findings are important because they demonstrate that the brain's processing of emotional language is not just about understanding the semantic content but also involves integrating affective information. This dynamic interplay between language, cognition, and emotion is crucial for understanding how everyday communication influences mental health and wellbeing. The results from this study offer new insights into how different types of language are processed by the brain, supporting the idea that wellbeing is deeply intertwined with how the brain integrates language with emotional processing systems.

The observed disruptions in the DMN following psychedelic administration could be interpreted in several ways: as a general relaxation of prior cognitive frameworks (REBUS model), as increased entropy within neural networks (Entropic Brain Hypothesis), or as disruptions specific to self-referential linguistic processes (HOLISTIC model). Each of these interpretations was carefully evaluated against the specific pattern of activation observed, evidence from prior studies, and theoretical coherence with our understanding of psychedelics and consciousness. Given this, the interpretation favouring the HOLISTIC model was justified due to its alignment with both the neural evidence provided in this thesis and its consistency with existing theories of language and consciousness.

Predictive Model: Linking Brain Activity and Wellbeing

One of the key contributions of this thesis was the development and application of a SVM model to predict wellbeing based on brain activity. The SVM model utilised fMRI data to analyse how different word categories influenced brain activity and correlated with self-reported wellbeing. By focusing on naturalistic stimuli, such as movies with complex language and emotional content, the model identified distinct patterns of brain activation that were predictive of participants' wellbeing scores.

The model showed significant accuracy in predicting wellbeing based on neural responses to positive and negative words, with activity in regions such as the ventral striatum (linked to reward processing) and the amygdala (associated with emotional regulation) emerging as key predictors. This finding is crucial, as it demonstrates the potential of ML techniques to link specific neural patterns to subjective emotional states, providing a data-driven approach to understanding how language and emotional processing contribute to mental health. These results not only support the idea that language is a distributed process but also highlight the predictive power of integrating neuroimaging with computational models.

Although all predictive models demonstrated substantial accuracy, suggesting genuine relationships between neural responses to language and subjective wellbeing, these findings should be interpreted with caution given the limitations of fMRI data. For instance, neural activity is inherently noisy and may reflect multiple cognitive processes beyond linguistic processing alone. Additionally, the generalisation of these predictive models to populations beyond those studied remains to be demonstrated.

Therefore, these predictive models should be viewed as exploratory tools highlighting potentially important neural markers rather than definitive indicators of wellbeing. Future work should explicitly test the robustness of these models across diverse populations and contexts, further validating their predictive capacity. Additionally, follow-up research incorporating behavioural and experiential measures will help clarify the precise cognitive or affective processes underlying the observed relationships.

Interconnectedness of Language and Consciousness

The neurobiology of consciousness is similarly complex, with numerous theories attempting to elucidate the mechanisms underlying conscious awareness. The GWT (Baars, 1997) and IIT (Tononi, 2004) propose frameworks for understanding how different neural activities coalesce to form a unified conscious experience. HOTs (Lau & Rosenthal, 2011) and Predictive Coding (Friston, 2010) offer additional perspectives on how the brain integrates sensory information and internal states to produce consciousness. These theories underscore the importance of integrating information across various brain networks, particularly the frontoparietal and thalamocortical systems, which are pivotal for maintaining a coherent stream of consciousness. The neural correlates of consciousness include regions such as the PFC and the PPC (Dehaene et al., 2011). These areas are essential for high-level cognitive functions and self-reflective thoughts, which are critical components of conscious experience. The dynamic interplay between the DMN and other brain networks facilitates the seamless integration of internal thoughts and external stimuli, contributing to our ongoing conscious awareness (Raichle, 2015).

Language, in this context, serves as a conduit for conscious thought, allowing for self-reflection and the construction of a narrative self (Dennett & Dennett, 1993). This intertwining of language and consciousness is evident in the phenomenon of inner speech and the role of language in shaping our self-concept and perception of reality (Fernyhough, 2008).

A significant theme emerging from this thesis is the deep interconnectedness between language and consciousness. Language not only facilitates communication and social interaction but also plays a pivotal role in the formation of the self and the narrative structure of personal identity (Schaller, 2008). Concepts such as inner speech, self-reflection, and embodied cognition illustrate how linguistic processes are integral to conscious experience (Barsalou, 2008; Gallagher, 2000; Morin, 2005).

Moreover, Chapter 2 of this research explores how alterations in language processing, as seen in ASCs, such as psychedelic experiences, correspond with changes in consciousness, highlighting the reciprocal relationship between these domains.

The results offer a deeper understanding of the NCCs by highlighting how conscious experiences of language, particularly those involving emotional content, are processed through broad and interconnected networks. However, it is important not to overstate these findings. While they inform our understanding of how language and consciousness are linked, they do not definitively prove a specific model of consciousness or language processing. Rather, they support the idea that consciousness and language are emergent phenomena involving the interaction of multiple brain networks (R. L. Carhart-Harris & Friston, 2010).

Psychedelics & Their Neural Effects

Psychedelics, particularly tryptamines like DMT, have been shown to profoundly alter conscious states and perceptual experiences. This thesis explored the neuroplastic changes induced by psychedelics. Psychedelics primarily act through the activation of 5-HT2A receptors, leading to downstream effects such as increased glutamate release and BDNF upregulation, which promote neuroplasticity (Carhart-Harris & Nutt, 2017; Vollenweider & Kometer, 2010). These changes are mirrored in the observed alterations in brain connectivity, particularly within the DMN. Psychedelic experiences often result in a transient disintegration and subsequent reintegration of the DMN, facilitating a more interconnected and less compartmentalised neural architecture (Carhart-Harris et al., 2014).

Our meta-analyses, in Chapter 2, suggests that psychedelics induce changes in the neurobiology of language, impacting regions associated with semantic processing and linguistic flexibility. These alterations in language-related brain regions may contribute to the psychological effects of psychedelics, such as ego-dissolution and increased connectedness, which are correlated with changes in the DMN and cerebellum activity. These findings align with behavioural research from the mid-20th century, which suggested that psychedelics enhance creative and associative thinking (MacLean et al., 2011). They also support the hypothesis that the neurobiology of language plays a crucial role in the profound alterations of consciousness induced by psychedelics. This mechanism is not only central to the ASCs induced by psychedelics but has significant implications for understanding how psychedelics can be used therapeutically, particularly in terms of enhancing psychological flexibility and reducing rigid, self-referential thought patterns (Griffiths et al., 2018).

Moreover, studies indicate that recovery of language functions is often correlated with improvements in consciousness levels in patients with disorders of consciousness. Aubinet et al., (2019) found that the re-emergence of command-following behaviours in patients is associated with the recovery of language and internal awareness networks, emphasising the critical role of language in assessing and understanding consciousness. Similarly, Bruno et al., (2012) discuss how language function impacts clinical assessments of consciousness, suggesting that deficits in language processing can obscure true levels of awareness. This interplay between language and consciousness is further supported by the notion that language facilitates the organisation of internal thoughts and experiences, thereby enhancing conscious awareness (Nelson and Fivush 2020).

The pharmacological modulation of consciousness is closely tied to language-related brain regions, reinforcing the idea that language is not only a tool for communication but also a fundamental component of conscious experience. The evidence suggests that understanding the neural correlates of language can provide deeper insights into the mechanisms of consciousness and its alterations through

Furthermore, the research in this thesis hypothesised that DMT would reduce activity in self-referential networks such as the DMN while enhancing activity in emotion-regulation and cognitive flexibility networks based on previous study, though we built on this, hypothesising that these changes would extend to language-processing networks. More precisely, we expected that DMT would reduce neural activity in regions associated with the processing of self-referential language (e.g., first-person pronouns) and negative emotional words, consistent with its role in ego dissolution and emotional detachment. Simultaneously, we hypothesised that DMT would enhance activity in regions supporting cognitive flexibility and social cognition, as evidenced by changes in brain activity in response to drive-related and social-related language. This integration of language into our hypotheses allows us to explore how DMT's influence on linguistic processing may contribute to broader improvements in mental health and wellbeing.

The preliminary results of the UNITy study largely support this hypothesis. Post-DMT, we observed a significant reduction in regions associated with the DMN when participants processed first-person words, consistent with the notion of ego dissolution commonly reported in psychedelic experiences (Palhano-Fontes et al., 2015). This reduction of regions associated with self-referential processing aligns with theories that DMT allows individuals to temporarily suspend rigid self-identity constructs, leading to enhanced emotional openness and cognitive flexibility. These effects were also reflected in the increased activation of regions involved in emotional regulation, such as the ACC, when processing positive words, suggesting that DMT facilitates a reorganisation of neural networks that support positive emotional engagement.

Further, DMT's impact on future-oriented words might suggest that the psychedelic experience enhances temporal flexibility, allowing individuals to engage more fluidly with future thinking and planning processes. This was suggested by the heightened activity observed in the precuneus and superior parietal lobule, regions involved in mental imagery and spatial planning (Schacter & Addis, 2007). These findings indicate that DMT may disrupt rigid temporal frameworks, enabling participants to break free from entrenched cognitive patterns and approach future-oriented tasks with greater openness.

Therapeutic Potential of Psychedelics

The alterations in brain activity observed post-DMT are particularly relevant for understanding the therapeutic potential of psychedelics. Psychedelics like DMT have been shown to induce neuroplastic changes that may contribute to their efficacy in treating mood disorders such as depression and anxiety (Ly et al., 2018).

The findings from this thesis suggest that DMT enhances the brain's processing of positive emotional stimuli, as evidenced by the increased activity in regions associated with reward processing when participants processed positive words. Conversely, the findings related to negative and negation words demonstrated a significant reduction in brain activity post-DMT, particularly in regions associated with negative emotion processing, such as the IFG. This suggests that DMT may facilitate emotional resilience by reducing the brain's sensitivity to negative stimuli and enhancing its responsiveness to positive emotional content (R. L. Carhart-Harris & Nutt, 2017).

Post-DMT, participants also exhibited increased activity in regions involved in social cognition, such as the supramarginal gyrus, when processing social words. This supports the hypothesis that psychedelics enhance social connectedness and empathy, which are important components of mental wellbeing (Griffiths et al., 2006)).

The SVM model applied in the DMT study further demonstrated its utility by predicting post-DMT well-being scores based on changes in brain activity.

Theoretical Integration: Language, Consciousness, and DMT

The combined findings from the meta-analyses, NNDb study, and UNITy study support a more integrated understanding of how language interacts with consciousness and how psychedelics like DMT further modulate these processes. The research demonstrates that language processing involves distributed neural networks, which are not confined to isolated regions but extend across sensory, emotional, and self-referential circuits. This finding challenges traditional views of language as being primarily localised in areas like Broca's or Wernicke's regions, aligning instead with theories like HOLISTIC, which argue for the multi-modal nature of language (Skipper, 2014)).

In addition, the results suggest that psychedelics have a role in modulating neural plasticity, potentially allowing for a more flexible engagement with language and self-referential processes. The reduction in regions associated with the DMN during first-person language processing post-DMT suggests that subjective ego dissolution may occur and might enable a loosening of rigid self-concepts, allowing for new ways of relating to emotional and cognitive experiences. This supports the hypothesis that DMT and similar psychedelics could be beneficial in treating psychiatric disorders where rigid thought patterns play a significant role, such as depression and PTSD (Cameron & Olson, 2018).

However, while the data robustly indicate alterations in FC post-DMT administration, the specific psychological mechanisms underlying these changes remain less well-defined. Competing interpretations might suggest that changes in language-related neural networks are secondary to broader neuroplasticity processes, or that they reflect more general changes in perceptual or attentional systems rather than language specifically. Regardless, based on the convergence of these findings—particularly the predictive modelling linking language-related neural patterns to wellbeing—the interpretation that DMT-induced neuroplasticity specifically modulates linguistic-cognitive processes related to emotional and self-referential processing is well-supported by the data and is coherent with existing literature on psychedelics and language.

At a broader level, these findings contribute to the ongoing discussion on the NCCs by showing how language serves as a gateway to understanding conscious experience. Through the processing of emotionally charged words, self-referential pronouns, and cognitive terms, we can observe how the brain constructs and modulates conscious awareness, especially under the influence of psychedelics like DMT.

Limitations and Future Directions

Despite the significant insights gained from this thesis, several limitations must be addressed. The sample size in the preliminary UNITy study was limited (*N* = 4), primarily due to delays caused by the COVID-19 pandemic and logistical challenges. This restricts the generalisability of the findings, and future studies should aim to recruit larger and more diverse samples to validate these results.

However, a more significant limitation is the correlational nature of much of the research. While the DMT administration offers a causal intervention, the observed relationships between brain activity and language processing, particularly their links to wellbeing, remain correlational. This leaves open the question of whether language-related changes directly contribute to shifts in consciousness and mental health or whether these are merely coactive phenomena without a unified underlying mechanism.

A key issue is the assumption that language, as we defined it, is distributed throughout the brain. This interpretation is contingent on what one considers "language." Critics might argue that regions associated with semantics or emotional processing are not strictly language-specific but part of broader cognitive or emotional networks. The distributed brain activity observed might reflect coactivation rather than an integrated language system. Future work should explore whether these brain regions are functionally unified during language processing or whether their involvement is driven by adjacent cognitive or emotional functions.

Although the meta-analytic portion in Chapter 2 of the thesis touched on multiple psychedelics, further research is needed to understand whether the observed effects on language and cognition generalise across different serotonergic compounds. This would provide a more comprehensive understanding of how psychedelics influence language, consciousness, and emotional processing.

Conclusion

In conclusion, this thesis has attempted to advanced our understanding of the distributed nature of language processing, providing support for the HOLISTIC theory and demonstrating that language comprehension engages broad neural networks beyond static "language regions." The integration of predictive modelling with neuroimaging has provided novel insights into how specific patterns of brain activity can be linked to emotional wellbeing, supporting the potential of computational approaches to predict mental health outcomes based on neural data.

The exploration of DMT's effects on language processing and wellbeing provides further support for how psychedelics can modulate brain networks involved in self-referential thought, emotion regulation, and social cognition. These findings contribute to the growing body of research on the therapeutic potential of psychedelics and provide a foundation for future studies to investigate how psychedelics can be used to treat mental health disorders by promoting neuroplasticity and emotional flexibility.

While these findings are promising, it is important to acknowledge the limitations of the current study. The current sample size in the UNITy study was relatively small, and further research is needed to replicate these results in larger and more diverse populations.

The predictive modelling approach utilised in this thesis offers exciting future possibilities for precision psychiatry, allowing for more personalised mental health interventions based on individual neural profiles. Moving forward, the integration of language, consciousness, and psychedelics will hopefully continue to offer valuable insights into the nature of human experience and the potential for innovative mental health treatments.

Supplementary Materials

Table S1.

Significantly greater activity for resting state classical psychedelic and ketamine neuroimaging studies compared resting state studies.

Primary Results					**Language-Related Results**							
Regions	SDM-Z	P	Voxels	Terms	Regions	x	y	z	SDM-Z	P	Voxels	Terms
					Left cerebellum, crus II	-26	-88	-34	4.892	0.000999987	729	
					Left cerebellum, crus I	-42	-74	-34	3.567	0.000999987	644	
					Left cerebellum, hemispheric lobule VIII	-8	-62	-50	4.269	0.000999987	462	
					Left cerebellum, hemispheric lobule VI, BA 37	-32	-54	-28	3.077	0.001999974	330	motor, premotor, movements, coordination, movement, imagery, tapping, sensorimotor, motor imagery
					Middle cerebellar peduncles	-28	-50	-36	3.182	0.000999987	241	dyslexia, autonomic, finger tapping
					Left fusiform gyrus, BA 37	-26	-40	-20	4.083	0.000999987	182	semantic, semantic memory, words
					Left cerebellum, hemispheric lobule VI	-30	-38	-38	3.303	0.000999987	158	motor function, olfactory, motor
					Left cerebellum, hemispheric lobule VIIB	-44	-52	-52	3.753	0.000999987	128	
					Left cerebellum, hemispheric lobule VI, BA 19	-32	-62	-28	3.21	0.000999987	107	motor, motor imagery, verbal working, motor function, premotor, rehearsal, movement, rhythm, imagery, working memory, load, movements
Left cerebellum, hemispheric lobule IX	4.892	0.001	3997		Left cerebellum, hemispheric lobule IV / V, BA 30	-22	-40	-20	3.875	0.000999987	16	autobiographical, memories, autobiographical memory, events, episodic, semantic

												memory, retrieval, recollection, navigation
					Right angular gyrus, BA 39	48	-66	48	4.999	0.000999987	597	mentalising, recognition memory, choose
					Right supramarginal gyrus, BA 40	46	-36	40	4.409	0.000999987	266	working memory, motor, premotor, visual, sequences, attentional, rehearsal, memory
					Right arcuate network, posterior segment	52	-50	4	4.2	0.000999987	191	action observation, motion, facial, perception, visual motion, actions, mirror, faces
					Right superior longitudinal fasciculus III	42	-38	38	4.629	0.000999987	134	working memory, calculation, spatial, maintenance, load, memory, premotor
					Right superior longitudinal fasciculus II	40	-60	36	4.634	0.000999987	112	semantic memory, memory
					Right middle occipital gyrus, BA 39	44	-66	28	5.147	0.000999987	78	autobiographical, default mode, default, memories, self referential, referential, remembering, autobiographical memory, retrieval
					Right angular gyrus, BA 40	54	-50	28	3.043	0.000999987	73	theory mind, mind, beliefs, mental states, memory performance
					Right angular gyrus	64	-54	26	3.273	0.001999974	72	theory mind, mind, belief, mental states, beliefs, mentalising, intentions, default network, reasoning, people, judgements
					Right postcentral gyrus, BA 3	48	-32	62	2.893	0.003000021	47	premotor, motor imagery, movements, motor, mirror, movement, touch, imagery
					Right middle temporal gyrus, BA 37	44	-60	14	3.787	0.000999987	39	motion, mental state, gaze, mentalising, social, objects
					Right superior temporal gyrus, BA 41	50	-42	20	3.938	0.000999987	27	watching, empathy, theory mind, empathic
					Right angular gyrus, BA 48	46	-50	28	3.992	0.000999987	21	theory mind, beliefs, mind, thinking, mental states, mentalising, older adults, episodic, social
					Right superior temporal gyrus	66	-50	22	3.676	0.000999987	17	belief, theory mind, thinking, mental states
Right inferior parietal (excluding supramarginal and angular) gyri, BA 40	5.721	0.001	3253	force, default network, motor	Right postcentral gyrus, BA 40	34	-36	48	3.305	0.000999987	7	premotor, motor, movements, sensorimotor, video, movements,

												coordination, mirror, watching, visuospatial, visual, motion, imagery, calculation
					Right median network, cingulum	8	-26	36	3.961	0.000999987	409	retrieved
					Left median cingulate / paracingulate gyri	-10	-46	34	4.738	0.000999987	321	retrieval, mind, episodic, older adults, retrieved, default, theory mind, default network, episodic memory, default mode, demand, memories, memory, aging, mental states, autobiographical
					Right median cingulate / paracingulate gyri, BA 23	10	-40	36	4.912	0.000999987	296	default network
					Right anterior cingulate / paracingulate gyri, BA 32	12	34	22	5.336	0.000999987	248	monitoring
					Left median network, cingulum	-6	16	24	2.599	0.003000021	224	fear, thought, conditioned, pain
					Left median cingulate / paracingulate gyri, BA 23	-6	-34	34	3.816	0.000999987	207	retrieval, items, recall, memories, episodic, memory
					Right precuneus	8	-44	46	4.45	0.000999987	190	
					Left median cingulate / paracingulate gyri	-10	-42	34	4.684	0.000999987	180	
					Corpus callosum	12	30	38	3.687	0.000999987	174	
					Right median cingulate / paracingulate gyri, BA 24	8	-2	42	2.946	0.000999987	167	
					Left median cingulate / paracingulate gyri, BA 24	-8	12	36	3.814	0.000999987	136	
					Right anterior cingulate / paracingulate gyri, BA 32	12	34	22	5.336	0.000999987	113	
					Left precuneus, BA 23	-10	-52	22	3.567	0.000999987	37	
Right anterior cingulate / paracingulate gyri, BA 32	5.387	0.001	3511	preferences								

					Right anterior cingulate / paracingulate gyri	6	18	24	3.79	0.000999987	24	
Left inferior frontal gyrus, opercular part, BA 44	5.511	0.001	3183	phonological, semantic, word, reading, words, language, linguistic, orthographic, lexical, demands	Left insula, BA 48	-40	2	-6	4.347	0.000999987	610	
					Left lenticular nucleus, putamen, BA 48	-26	14	-8	4.62	0.000999987	198	
					Left precentral gyrus, BA 6	-52	6	16	4.638	0.000999987	153	phonological, pseudowords, articulatory, rehearsal, speech
					Left inferior frontal gyrus, opercular part, BA 48	-50	16	20	4.785	0.000999987	133	syntactic, sentences, language, semantic, phonological
					Left frontal aslant tract	-42	10	10	3.873	0.000999987	119	rehearsal, nouns, word, phonological
					Left striatum	-28	-4	-2	3.041	0.001999974	111	
					Left superior longitudinal fasciculus III	-38	8	12	4.165	0.000999987	99	
					Left inferior frontal gyrus, orbital part, BA 47	-28	30	-16	3.16	0.003000021	94	
					Left middle frontal gyrus, BA 44	-44	14	40	4.479	0.000999987	72	
					Left inferior frontal gyrus, triangular part, BA 47	-48	20	0	4.793	0.000999987	51	
					Left lenticular nucleus, putamen	-26	0	4	3.573	0.000999987	49	
					Left temporal pole, superior temporal gyrus, BA 38	-54	6	-12	3.342	0.003000021	43	
					Left superior temporal gyrus, BA 48	-44	0	-8	3.432	0.000999987	42	
Right middle frontal gyrus, BA 8	4.587	0.000999987	2265		Right middle frontal gyrus, BA 46	36	36	26	4.423	0.000999987	481	

Right middle frontal gyrus, BA 9	24	28	42	4.129	0.000999987	389
Right superior frontal gyrus, dorsolateral, BA 8	26	18	46	4.235	0.000999987	260
Right middle frontal gyrus, BA 8	30	22	54	3.034	0.001999974	192
Right middle frontal gyrus, BA 6	34	0	52	4.181	0.000999987	155
Right superior frontal gyrus, dorsolateral, BA 9	24	36	42	3.892	0.000999987	150
Right precentral gyrus, BA 6	42	0	50	3.831	0.000999987	130
Right middle frontal gyrus	26	40	42	3.944	0.000999987	90
Right middle frontal gyrus, BA 45	46	32	30	3.02	0.004999995	33
Right middle frontal gyrus, BA 44	42	16	40	3.343	0.001999974	31
Right inferior frontal gyrus, triangular part, BA 45	44	32	26	3.954	0.001999974	26
Right inferior frontal gyrus, triangular part, BA 48	44	26	28	3.176	0.001999974	10
Left middle frontal gyrus, BA 46	-38	46	28	4.399	0.001999974	369
Corpus callosum	-34	42	12	4.178	0.000999987	135
Left middle frontal gyrus, BA 10	-30	60	14	4.546	0.000999987	115
Left middle frontal gyrus, BA 9	-24	34	42	3.303	0.005999982	29
Left superior frontal gyrus, dorsolateral, BA 10				4.956	0.000999987	935

				Left inferior frontal gyrus, triangular part, BA 48	-42	26	22	2.975	0.004999995	18
Right precuneus, BA 7	4.312	0.001999974	209							
Right cerebellum, hemispheric lobule VI, BA 37	4.679	0.005999982	22							
Corpus callosum	3.587	0.00999999	1							

Note. *There were no regions significantly more active for the placebo condition. Activity is presented as the regions of the peak voxels in resulting clusters (left columns) and specific subregions that overlap with large-scale term-based neuroimaging meta-analyses of 'speech' and 'language' (right columns). Specifically, 'Regions' are the labels from X atlas, SDM-Z is the Seed-based d Mapping Z score, with 'P' being the voxel probability threshold: p = 0.001. 'Voxels' refers to the number of voxels in each resulting cluster and peak height threshold: p = 0.001, 'X Y Z' to the Montreal Neurological Institute (MNI) coordinates for the peak voxel in those clusters, , and 'Terms,' indicate the term-based meta-analytic neuroimaging meta-analyses associated with those peak coordinates according to Neurosynth, along with the z score of the terms in relation to the regions. All results are corrected for multiple comparisons using a TFCE (threshold free cluster enhancement) thresholded at α >= .01 and an additional cluster extent threshold of >= 100 voxels.*

Table S2.

Significantly greater activity for task based classical psychedelic and ketamine neuroimaging studies compared resting state studies.

Primary Results					Language-Related Results							
Regions	SDM-Z	P	Voxels	Terms	Regions	x	y	z	SDM-Z	P	Voxels	Terms
Right anterior cingulate / paracingulate gyri, BA 32	8.243	~0	4851	abuse, gain, reward, behavior, losses, error, errors, control, discriminative, pain	Right supplementary motor area, BA 6	2	4	56	7.179	0.000999987	330	execution, eye fields, sensorimotor, movement, task, tapping, sequential, imagery, action
					Right anterior cingulate / paracingulate gyri, BA 32	10	40	16	6.594	0.000999987	303	reward, gain
					Left median cingulate / paracingulate gyri, BA 24	-2	8	40	8.054	0.000999987	246	pain, painful, somatosensory, motor, ratings, tapping
					Right median cingulate / paracingulate gyri, BA 24	2	0	42	7.314	0.000999987	227	motor, somatosensory, pain, movement, imagery
					Left superior frontal gyrus, medial, BA 8	-2	30	52	7.755	0.000999987	211	categorisation, semantic
					Left supplementary motor area, BA 6	-10	12	60	7.318	0.000999987	197	sentence, sentences, read, comprehension, reading
					Right anterior cingulate / paracingulate gyri, BA 32	2	42	6	6.594	0.000999987	176	default, dmn, connectivity, limbic, resting, reward
					Right median network, cingulum	6	10	34	6.796	0.000999987	154	pain, painful, motor, noxious, somatosensory, fear
					Left supplementary motor area, BA 8	-4	22	54	8.141	0.000999987	153	semantic, chinese, language
					Left anterior cingulate / paracingulate gyri, BA 32	0	40	22	7.157	0.000999987	146	discrimintative
					Left superior frontal gyrus, medial orbital, BA 11	-4	38	-12	7.952	0.000999987	135	autobiographical memory, money, decision, choice, social cognition, rewards, reward, autobiographical, social, mentalising, choose, personal, pain

Left median cingulate / paracingulate gyri, BA 23	0	-10	34	7.055	0.000999987	126	pain
Right superior frontal gyrus, dorsolateral, BA 9	14	48	40	7.26	0.000999987	118	photographs, chosen, affective, social
Left anterior cingulate / paracingulate gyri, BA 24	0	36	18	7.379	0.000999987	117	intense, cognitive emotional, affective, pain, reward
Left supplementary motor area	2	14	44	7.301	0.000999987	112	verbal, phonological
Left supplementary motor area, BA 32	-2	14	44	7.103	0.000999987	110	word, phonological, verbal, visual word, english
Left anterior cingulate / paracingulate gyri, BA 11	-2	32	-10	7.961	0.000999987	95	valence, reinforcement, arousal, reward, autobiographical, noxious
Left superior frontal gyrus, medial, BA 9	-4	48	40	6.542	0.000999987	93	thoughts, comprehension, social, language
Right superior frontal gyrus, medial, BA 9	4	52	42	6.478	0.000999987	79	theory mind, social, mind, mental states, beliefs
Right superior frontal gyrus, medial orbital, BA 10	10	56	-2	5.176	0.001999974	67	reward. default mode, mood, social, mind, self referential, monetary, memories, autobiographical
Right anterior cingulate / paracingulate gyri, BA 11	10	42	4	5.806	0.000999987	66	value, limbic, pictures, subsequent memory, mood, food
Right superior frontal gyrus, medial, BA 8	4	22	44	8.08	0.000999987	62	word
Left median cingulate / paracingulate gyri, BA 32	-6	12	42	6.826	0.000999987	50	pain, motor, task, painful, finger tapping, premotor, speech production, reading, phonological
Right supplementary motor area, BA 8	2	18	52	7.455	0.000999987	47	task, working memory, demands, load, maintenance, letter, verbal working, verbal, tapping, memory, phonological, sentences, motor
Right middle frontal gyrus	28	34	46	5.086	0.001999974	24	default, default mode

					Right superior frontal gyrus, medial, BA 10	10	60	0	4.717	0.004999995	21	autobiographical memory, dmn, default mode, resting
Right middle temporal gyrus, BA 21	7.089	0.001	1894	temporal, unexpected, discriminative, speaker	Right insula, BA 48	38	-20	10	6.819	0.000999987	347	auditory, sound, speech, sounds
					Right middle temporal gyrus, BA 21	62	-20	-16	6.384	0.000999987	197	default network, default, default mode
					Right lenticular nucleus, putamen, BA 48	26	10	-4	6.031	0.000999987	160	reward, gains, chronic pain, motor, pain, losses, limbic, sensorimotor, monetary, anticipation, noxious
					Right inferior frontal gyrus, opercular part, BA 48	48	14	10	6.304	0.000999987	134	premotor, motor, sequence
					Right rolandic operculum, BA 48	36	-20	16	6.097	0.000999987	94	pain, painful, noxious, sensation, chronic pain, anxiety, ratings, gain, somatosensory
					Corpus callosum	52	-12	-2	5.759	0.000999987	87	auditory, listening, speech, acoustic, sounds, listened, pitch, music, primary auditory, sound, speech perception, musical, spoken, tone, noise, multisensory, heard, nouns, production
					Right superior temporal gyrus, BA 48	58	-4	2	5.3	0.001999974	69	speech, speech perception, listening, vocal, speech production
					Right striatum	26	12	4	5.248	0.001999974	60	motor, force, parkinson, pressure, noxious, losses, reward, somatosensory, sensorimotor
					Right superior temporal gyrus, BA 22	54	-20	-4	6.68	0.000999987	59	listening, speech, voice, speech perception, spoken
					Right inferior frontal gyrus, opercular part, BA 44	52	12	14	6.024	0.000999987	53	none
					Right inferior frontal gyrus, triangular part, BA 45	48	18	4	6.683	0.000999987	42	heard, speaker
					Right superior temporal gyrus, BA 21	66	-12	-6	4.914	0.003000021	29	sounds, auditory, spoken, speech, listening, words, voice, heard, listened, phonological, language network, language, lexical, sound, linguistic, audiovisual, languages, hearing, sentence, pitch, language comprehension, acoustic, speaking, word, speaker, speech production, vocal
					Right insula, BA 47	40	26	2	5.337	0.001999974	25	gain, task

					Right inferior network, inferior fronto-occipital fasciculus	28	16	2	5.184	0.001999974	25	likelihood, gain, task
					Right arcuate network, posterior segment	58	-38	-4	6.793	0.000999987	20	auditory visual, auditory, language
					Right inferior frontal gyrus, triangular part, BA 47	46	26	-2	5.218	0.001999974	20	social, visual word
					Right superior temporal gyrus	58	0	4	5.24	0.001999974	10	pitch, vocal, auditory
					Right temporal pole, superior temporal gyrus, BA 38	38	4	-22	5.197	0.001999974	8	emotional, unpleasant, anxiety disorders, fear, anxiety, pleasant, pictures, negative emotions, valence, food, arousal, belief,
					Right frontal orbito-polar tract	26	24	-12	5.317	0.001999974	8	punishment, reward, regulate, heart rate, emotional,
					Right superior longitudinal fasciculus III	28	16	8	5.193	0.001999974	8	gain, motor, pain, task
Left striatum	7.513	0.001	1531	sensorimotor, movement, movements, execution, sensations, finger tapping, handed, parkinson disease, tapping, dominant	Left insula, BA 48	-36	6	6	7.067	0.000999987	418	pain, painful, noxious, limbic, arousal, motor
					Left lenticular nucleus, putamen, BA 48	-30	-8	0	7.45	0.000999987	146	speech production
					Left striatum	-22	16	-8	6.535	0.000999987	134	incentive, losses, monetary incentive, reward, anticipation, motivational
					Left rolandic operculum, BA 48	-54	0	4	5.022	0.001999974	43	motor, painful, pain, somatosensory, noxious, imagery, video, vocal, production, movement
					Left superior temporal gyrus, BA 48	-52	0	0	5.158	0.001999974	36	auditory, vocal, speech, production
					Left inferior network, inferior fronto-occipital fasciculus	-26	18	0	5.209	0.001999974	23	working memory, task, tasks, working, cognitive, memory, lexical
					Left olfactory cortex, BA 48	-20	4	-14	6.522	0.000999987	19	reward. emotional, monetary, fear, incentive, ptsd, fearful, emotion regulation, stress, dopamine, mesolimbic, expressions, gambling, conditioning, valence

					Left parahippocampal gyrus, BA 34	-16	0	-18	6.601	0.000999987	12	emotional, fear, neutral, facial, pictures, reward, fearful, emotionally, faces, emotional, ratings, valence, expressions, happy, arousal, conditioned, regulation, threatening, limbic, stress, salient, social
					Left heschl gyrus, BA 48	-38	-18	10	5.293	0.001999974	10	auditory, tone, pitch
Right cerebellum, crus I	6.995	0.001	1540	conditioning, classical, symbolic, verbs, neutral pictures	Right cerebellum, crus I	34	-74	-32	6.632	0.000999987	534	paired, experiencing, motor,
					Right cerebellum, hemispheric lobule VI, BA 37	30	-44	-30	6.579	0.000999987	299	motor, movement, premotor, sensorimotor
					Right fusiform gyrus, BA 37	42	-54	-22	6.336	0.000999987	117	categories, category, social, social interaction, voice
					Right cerebellum, hemispheric lobule VI, BA 19	42	-66	-22	5.721	0.000999987	94	language network, reading, word form, perception, phonological
					Right cerebellum, crus II	28	-78	-40	5.634	0.000999987	87	thinking, mental states, mentalizing, words, semantic memory
					Right cerebellum, crus I, BA 19	28	-76	-26	6.276	0.000999987	67	mind, speech production
					Right cerebellum, hemispheric lobule VI	32	-56	-34	5.437	0.001999974	62	rehearsal, verbal working, working, working memory, navigation, memory, sequence, motor, load, phonological, premotor, loop, imagery
Left middle frontal gyrus, BA 9	7.774	0.001	1312	preparation	Left middle frontal gyrus, BA 46	-40	40	24	7.162	0.000999987	311	working memory, working, memory, older adults, tasks
					Left inferior frontal gyrus, triangular part, BA 48	-40	24	28	4.93	0.003000021	107	semantic, word, reading
					Corpus callosum	-52	0	24	6.937	0.000999987	100	premotor, phonological, movements, motor, language, sensorimotor, articulatory, lexical, speech production, planning, speech, words
					Left inferior frontal gyrus, opercular part, BA 44	-56	16	20	5.91	0.000999987	80	sentences, language, syntactic, phonological, word
					Left precentral gyrus, BA 6	-58	0	38	5.268	0.001999974	74	production, speech, speech production

					Left middle frontal gyrus, BA 45	-40	40	18	6.349	0.000999987	52	rules, word
					Left inferior frontal gyrus, triangular part, BA 44	-54	18	26	6.164	0.000999987	45	sentence, semantic, phonological, word, language
					Left postcentral gyrus, BA 43	-60	-2	26	5.891	0.000999987	41	production, speech production, vocal, speech
					Left precentral gyrus, BA 44	-52	6	32	6.119	0.000999987	40	phonological, reading, rehearsal, letters, english
					Left inferior frontal gyrus, opercular part, BA 48	-48	14	18	6.806	0.000999987	39	language, word, syntactic, lexical, sentences
					Left precentral gyrus, BA 4	-58	0	30	6.085	0.000999987	22	rehearsal, production, repetition, repetition suppression, speech production
					Left frontal inferior longitudinal fasciculus	-46	16	22	6.872	0.000999987	10	language, sentences, semantic, linguistic, comprehension
Left postcentral gyrus, BA 2	6.914	0.001	680	finger, grasping, finger movements, finger tapping, tapping, sequential, movements, preparation, calculation, demands	Left inferior parietal (excluding supramarginal and angular) gyri, BA 40	-32	-48	52	6.263	0.000999987	142	premotor, movements, spatial attention, tasks, visual, motor, videos, attention,
					Left superior parietal gyrus, BA 7	-24	-68	50	6.092	0.000999987	105	letter, reading
					Left inferior parietal (excluding supramarginal and angular) gyri, BA 2	-48	-32	40	6.854	0.000999987	103	motor, premotor, movements, action, tasks, force, grasping, coordination, sensorimotor, semantic
					Left inferior parietal (excluding supramarginal and angular) gyri, BA 7	-30	-58	48	5.395	0.001999974	54	word, reading, phonological, words, word form
					Left inferior parietal (excluding supramarginal and angular) gyri, BA 3	-58	-24	46	6.637	0.000999987	37	somatosensory, motor, action, video, mirror, movements
					Left angular gyrus, BA 39	-42	-66	44	5.709	0.000999987	33	memory retrieval, retrieval, solving, default network, episodic, memory, thinking

Right supramarginal gyrus, BA 2	7.634	0.001	639	motor, tasks, finger, spatial, visual, execution, serial, movements, sequences, planning	Left supramarginal gyrus, BA 2	-56	-28	38	6.86	0.000999987	32	action, actions, premotor, motor, somatosensory, movements, empathy, painful, calculation, mirror, abstract, body, imitation, gestures
					Left angular gyrus, BA 7	-38	-70	42	5.68	0.000999987	24	semantic, lexical, words
					Right postcentral gyrus, BA 3	54	-24	42	7.521	0.000999987	158	somatosensory, motor, sensorimotor, premotor, painful, movements, noxious, sensory
					Right supramarginal gyrus, BA 2	56	-26	38	6.562	0.000999987	78	somatosensory, motor, movements, premotor, mirror, painful, sensorimotor, noxious, empathy, pain, movement
					Right precentral gyrus, BA 4	50	-16	44	7.242	0.000999987	49	somatosensory, motor, sensorimotor, sensory, belief, reorganisation
					Right precentral gyrus, BA 6	56	-8	46	5.302	0.001999974	44	speech, lexical, vocal, auditory, spoken
					Right postcentral gyrus, BA 2	44	-32	48	6.876	0.000999987	41	premotor, motor, planning, movements, tasks, sensorimotor, sequential, sequence, loop, multisensory, coordination, visual
					Right supramarginal gyrus, BA 48	52	-34	30	5.316	0.001999974	36	belief, force, somatosensory, premotor, noxious, pain, movements, motor
					Right precentral gyrus, BA 3	56	0	46	5.124	0.001999974	10	music, auditory, listening, speech, vocal
Right inferior occipital gyrus, BA 18	6.116	0.001	303	chinese, reading, navigation, orthographic, faces	Right lingual gyrus, BA 18	20	-96	-10	5.747	0.000999987	73	reading, languages
					Right calcarine fissure / surrounding cortex, BA 18	22	-98	-4	5.619	0.000999987	66	reading, videos
					Right inferior network, inferior longitudinal fasciculus	22	-88	0	5.291	0.001999974	41	reading, chinese, english, bilinguals, speakers
					Right inferior occipital gyrus, BA 19	32	-88	-12	5.679	0.000999987	31	faces, visual, angry
					Right calcarine fissure / surrounding cortex, BA 17	12	-98	-2	5.169	0.001999974	16	categories, lingual

Left middle frontal gyrus, orbital part, BA 47	6.495	0.001	202	reasoning, solving, rules, autobiographical	Left middle frontal gyrus, orbital part, BA 11	-30	50	-12	5.691	0.000999987		relational
Right middle occipital gyrus, BA 39	5.695	0.001	168	visual motion, navigation, mentalizing, contextual, motion, attention, encoding retrieval, retrieval, visual	Right middle temporal gyrus, BA 37	48	-64	10	5.695	0.000999987	88	motion, video, actions, visual, gestures, perception, body, mirror, social, early visual, mentalising
					Right middle temporal gyrus, BA 37	52	-62	-2	5.606	0.000999987	34	motion, visual, viewing, movements, perception, vision, premotor
					Right middle temporal gyrus, BA 39	46	-72	16	5.481	0.000999987	23	mentalising, visual, mental imagery, motion
Left inferior temporal gyrus, BA 20	6.056	0.001	166	faces. face, visual word, words, selective, reading, language comprehension, pseudowords, recognition, expertise	Left fusiform gyrus, BA 37	-32	-42	-18	5.346	0.001999974	59	
					Left inferior network, inferior longitudinal fasciculus	-30	-46	-14	5.118	0.001999974	34	visual, remembered, category, perception, navigation, memory
					Left inferior temporal gyrus, BA 37	-46	-44	-28	5.796	0.000999987	27	visual word, word form, verbs, word recognition, nouns
Right temporal pole, superior temporal gyrus	5.939	0.001	160	hypoactivation, taste	Right inferior frontal gyrus, orbital part, BA 38	30	20	-24	5.474	0.000999987	37	progressive
					Right temporal pole, superior temporal gyrus, BA 38	46	20	-18	5.214	0.001999974	30	sentences, emotional
					Right insula, BA 38	32	16	-20	5.401	0.001999974	21	social
					Right temporal pole, middle temporal gyrus, BA 38	46	14	-28	5.172	0.001999974	14	mental states, semantic memory, language, social cognitive
Left striatum	5.916	0.001	111	reward, monetary, incentive, anticipation, incentive delay, gain ,monetary incentive, rewards, motivation, monetary reward	Left anterior thalamic projections	-12	12	6	5.646	0.000999987	70	incentive, reward, monetary, anticipation, rewards, motivation, dopamine, memory retrieval

Left middle temporal gyrus, BA 20	5.822	0.000999987	77	default mode, default, disability, semantic, recollection	Left middle temporal gyrus, BA 21	-60	-24	-14	5.658	0.000999987	34	
Left precentral gyrus, BA 9	5.809	0.000999987	65	memories, memory, episodic, retrieval, bilinguals, semantic, task	Left middle frontal gyrus, BA 9	-42	10	50	5.671	0.000999987	15	sentence, comprehension, mental states, language, episodic, linguistic, tasks, autobiographical, sentences, semantic, retrieval, syntactic, recollection
Right middle frontal gyrus, BA 45	5.793	0.000999987	47	noxious, painful, working, preparation, tasks		42	44	18				
Corpus callosum	5.65	0.000999987	42	touch, movement, motor, reaching, sensorimotor	Left hand superior U tract	-30	-32	52	5.639	0.000999987	25	sensorimotor, motor, movement, premotor, reaching, coordination, pain
(undefined)	5.547	0.000999987	42	navigation, episodic, events, lingual, episodic memory, autobiographical memory, visual	Right lingual gyrus, BA 27	16	-44	0	5.005	0.003000021	8	remembering, episodic, episodic memory, navigation, encoding, memory, memories, autobiographical
Left middle frontal gyrus, orbital part, BA 11	5.383	0.001999974	38	taste, reward, food, negative feedback, decision making, reinforcement, monetary reward, valence, heart rate, sensation, olfactory		-20	36	-18				
Left middle frontal gyrus	5.789	0.000999987	30	memory, retrieval, load, rule, working memory		-32	56	10				
Right lingual gyrus, BA 18	5.869	0.000999987	30	tracking, visual, production, words		14	-72	-12				
Right inferior frontal gyrus, opercular part	5.203	0.001999974	26	premotor, motor, movements, motor imagery, gestures, movements, tasks, lateralised, planning, mirror, visuomotor, visually, imagery	Right precentral gyrus, BA 6	58	2	24	5.015	0.003000021	11	motor, premotor, production, speech production, oral, movements, speech

Right middle occipital gyrus, BA 19	5.668	0.000999987	25	attention, task, preparatory, visual, letter, attentional, word form, tasks, chosen, visual word, memory			
Left median network, cingulum	5.654	0.000999987	20	episodic, retrieval, retrieved, memory, autobiographical, memories, episodic memory, recognition memory, goals, autobiographical memory, nouns			
Right cuneus cortex, BA 18	5.645	0.000999987	19	sighted, semantically, visual, reading	16	-90	24
Left insula, BA 47	5.529	0.000999987	19				
Right middle occipital gyrus, BA 39	5.011	0.003000021	16	motion, navigation, episodic memory	40	-76	24
Left anterior thalamic projections	5.027	0.001999974	14	task	-12	-4	10
Left middle frontal gyrus, BA 8	5.697	0.000999987	13	heard	-28	12	46
Right cerebellum, hemispheric lobule IV / V, BA 19	5.027	0.001999974	13	motor, sensorimotor, movement, force	14	-52	-12
Left superior longitudinal fasciculus II	5.636	0.000999987	11	lexical, aging, semantics, older adults, language, word, english	-34	12	32
Left superior frontal gyrus, medial, BA 32	5.287	0.001999974	8	craving, self reported, ratings	-12	40	18
Left middle occipital gyrus, BA 18	5.148	0.001999974	8	visual, matching	-26	-90	20
Right middle frontal gyrus, BA 46	4.869	0.003000021	7	noxious	30	48	20
Right inferior frontal gyrus, orbital part, BA 47	5.149	0.001999974	6	olfactory, food, semantic, retrieval, episodic	30	36	-10

Left inferior network, uncinate fasciculus	5.16	0.001999974	6	encoding, conditioning	-20	22	-14
Right precuneus, BA 7	4.93	0.003000021	6	memory, working memory	4	-64	50
Corpus callosum	4.908	0.003000021	6	blind, sighted, lingual, encode, visual	18	-82	26
Left caudate nucleus, BA 25	5.112	0.001999974	6	reward, rewards, reward anticipation	-6	20	-6
Right parahippocampal gyrus, BA 36	5.164	0.001999974	5	neutral, expressions, fear, memory encoding, emotional, valence, conditioned, memory	28	-4	-32
Right median network, cingulum	5.159	0.001999974	4	autism, default network	10	-44	24
Right inferior frontal gyrus, orbital part, BA 11	4.999	0.003000021	3	reward, food, eating, regulation, emotional, anxiety, conditioning, emotional information, reward anticipation	26	32	-12
Left middle frontal gyrus, orbital part, BA 46	4.999	0.003000021	3	relational, reasoning, rules, semantic, memory retrieval, phonological, word	-44	46	-2
Left supramarginal gyrus, BA 40	4.802	0.004000008	3	response inhibition, videos, pain	-64	-38	32
Right middle frontal gyrus, BA 46	4.799	0.004000008	2	noxious, painful, loop	38	54	14
Right superior frontal gyrus, medial, BA 10	4.788	0.004000008	2	autobiographical, semantic memory	10	66	0
Right calcarine fissure / surrounding cortex, BA 18	4.822	0.003000021	2	visual, psuedowords, reading, word, words	18	-92	2
Right inferior network, inferior longitudinal fasciculus	4.759	0.004000008	2	concentration	34	-2	30

Right middle frontal gyrus, BA 9	4.711	0.004999995	2	emotional responses, memory, working, working memory, semantic memory	36	14	46
Right inferior network, inferior longitudinal fasciculus	4.713	0.004999995	2		42	-2	-34
Right lingual gyrus, BA 18	4.634	0.007000029	2	lingual	14	-64	-10
Right precuneus, BA 5	4.651	0.007000029	2	spatial attention, orienting, attention, visual attention, navigation	8	-54	56
Right anterior thalamic projections	4.606	0.008000016	2	imagine	18	20	14
Left middle frontal gyrus, BA 9	5.064	0.001999974	1	autobiographical, autobiographical memory, episodic, referential, self referential, default network, default mode	-24	24	42
Corpus callosum	4.994	0.003000021	1	faces, facial expression	52	-40	-14
Right precentral gyrus, BA 44	4.951	0.003000021	1	premotor, task, mirror, imitation, visual, real world, calculation, movements	52	10	32
Left median cingulate / paracingulate gyri	4.817	0.003000021	1	tapping, remembered, motor network	-12	-12	42
Right parahippocampal gyrus, BA 28	4.747	0.004999995	1	neutral, fear, emotional, pictures, empathy, ptsd, valence, expression, arousal	22	2	-30
Left cerebellum, crus II	4.661	0.005999982	1	sighted	-6	-86	-28
Right middle occipital gyrus, BA 39	4.658	0.005999982	1	default network, autobiographical, default, retrieval, episodic, memories, semantic, episodic memory	48	-72	26

Left cerebellum, hemispheric lobule IV / V, BA 30	4.62	0.007000029	1	loop, rewarding, autobiographical	-10	-36	-12
Left precuneus, BA 23	4.609	0.008000016	1	autobiographical, episodic, default, default mode, mentalising, episodic memory, memories, retrieval, autobiographical memory, beliefs, referential, social, theory of mind, remembering, semantic, mind, memory	-4	-62	18
Left precentral gyrus, BA 6	4.607	0.008000016	1	premotor, motor, motor imagery, movements, rules, coordination, imagery, imitation, task, tasks, reading, planning, preparation, sensorimotor, working memory, language, movement	-52	4	38
Right superior occipital gyrus, BA 18	4.601	0.008000016	1	sighted, touch, blind, social interaction	20	-92	30

Note. There were no regions significantly more active for the placebo condition. Activity is presented as the regions of the peak voxels in resulting clusters (left columns) and specific subregions that overlap with large-scale term-based neuroimaging meta-analyses of ‘speech’ and ‘language’ (right columns). Specifically, ‘Regions’ are the labels from X atlas, SDM-Z is the Seed-based d Mapping Z score, with ‘P’ being the voxel probability threshold: p = 0.001. ‘Voxels’ refers to the number of voxels in each resulting cluster and peak height threshold: p = 0.001, ‘X Y Z’ to the Montreal Neurological Institute (MNI) coordinates for the peak voxel in those clusters, , and ‘Terms,’ indicate the term-based meta-analytic neuroimaging meta-analyses associated with those peak coordinates according to Neurosynth, along with the z score of the terms in relation to the regions. All results are corrected for multiple comparisons using a TFCE (threshold free cluster enhancement) thresholded at α >= .01 and an additional cluster extent threshold of >= 100 voxels.

Table S3

The number of words in each of the 16 predictive word categories broken down by the specific movie.

Movie	Concrete	Cognitive	Drive	First	Future	Lifestyle	Negation	Negative	Past	Perception	Physical	Positive	Present	Second	Social	Third
12 Years A Slave	32	78	86	168	39	107	44	37	67	56	67	34	55	171	42	99
500 Days of Summer	457	276	118	492	40	129	59	36	138	229	114	48	153	412	342	102
Back to the Future	494	318	162	253	48	121	63	24	166	261	76	17	143	458	349	121
Citizen Four	917	574	322	319	62	240	68	32	202	439	53	35	196	410	517	68
Little Miss Sunshine	426	237	199	226	28	121	49	24	122	289	128	15	166	398	350	121

Pulp Fiction	356	465	262	425	84	228	130	67	251	432	394	50	277	720	649	194
Split	439	260	124	259	29	98	51	55	131	232	117	27	134	367	320	113
The Prestige	614	392	199	331	76	153	102	41	186	307	116	50	207	548	482	165
The Shawshank Redemption	823	417	226	286	74	275	105	49	231	431	244	44	202	436	497	218
The Usual Suspects	543	314	203	283	50	167	76	31	189	292	156	16	167	448	439	227
Total	5101	3331	1901	3042	530	1639	747	396	1683	2968	1465	336	1700	4368	3987	1428

Table S4

The number of words in each of the 15 predictive word categories broken down by the specific movie.

Movie	Cognitive	Drive	First	Future	Lifestyle	Negation	Negative	Past	Perception	Physical	Positive	Present	Second	Social	Third
Cocktail	611	143	582	165	219	250	48	244	837	141	139	267	225	336	163
Lost in Translation	159	25	116	18	18	40	9	32	73	35	38	129	110	87	17
Withnail and I	523	188	193	106	175	279	127	213	680	239	176	134	91	364	185
Total	1293	356	891	289	412	569	184	489	1590	415	353	530	426	787	365

Note. Due to concrete not being significant in the NNDb movies, we excluded it from this UNITy dataset.

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