Assessing the Impact of Daily Life Events on Depression Symptomatology and the Neural Correlates of State & Trait Depression within Resting-State Networks as deduced by Probabilistic Functional Modes

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Assessing the Impact of Daily Life Events on Depression Symptomatology and the Neural Correlates of State & Trait Depression within Resting-State Networks as deduced by Probabilistic Functional Modes

by

Rosie Dutt

A dissertation presented to the McKelvey School of Engineering of Washington University in partial fulfillment of the requirements for the degree of Doctor of Philosophy

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List of Abbreviations

Amps   Amplitudes
ANOVA  Analysis of Variance
ANCOVA Analysis of Covariance
BOLD   Blood Oxygenation Level Dependent
CEN    Central Executive Network
DMN    Default Mode Network
DSM-V  Diagnostic and Statistical Manual of Mental Health Fifth Edition
EEG    Electroencephalogram
FDR    False Discovery Rate
fMRI   functional Magnetic Resonance Imaging
FPN    Frontoparietal Network
FWHM   Full Width at Half Maximum
GHQ-12 General Health Questionnaire
HPA    Hypothalamic Pituitary Adrenal
HRF    Hemodynamic Response Function
ICA    Independent Component Analysis
ICD-10 International Classification of Diseases Edition 10
K-NN   K-Nearest Neighborhood
LCU    Life Changing Unit
MDD    Major Depressive Disorder
MNI    Montreal Neurological Institute
MRI    Magnetic Resonance Imaging
MSE  Mean Squared Error
Netmats  Network Matrices
PCC  Posterior cingulate cortex
PHQ-9  Patient Health Questionnaire
PROFUMO  Probabilistic Functional Modes
RDS-4  Recent Depression Score
ROI  Region of Interest
rs-fMRI  Resting State functional Magnetic Resonance Imaging
RSN  Resting State Networks
SCA  Seed-based Correlation Analysis
SN  Salience Network
SRRS  Social Readjustment Rating Scale
UES  Unpleasant Events Schedule
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Washington University in St. Louis
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ABSTRACT OF THE DISSERTATION

Assessing the Impact of Daily Life Events on Depression Symptomatology and the Neural Correlates of State & Trait Depression within Resting-State Networks as deduced by Probabilistic Functional Modes

by
Rosie Dutt
Doctor of Philosophy in Imaging Science
Washington University in St. Louis, 2023
Professor Janine Bijsterbosch, Chair

In our everyday lives, we experience several life events that are either positive in nature (uplifting events) or irritating in nature (hassling events). Independently, these events may not impact an individual’s mood, but together they may accumulate to do so. As such, one would hypothesize that a greater number of hassles experienced would lead to a higher depression level, whilst a greater number of uplifts experienced would lead to a lower depression level. The first Aim of this thesis is to investigate the association between cumulative life events and depression using a linear regression model. The findings revealed that life events (combined cumulative hassles and uplifts) explain 31% of the variance in depression scores, with uplifts related to the ability to confide and health-related hassles being the greatest contributors in relation to the proportion of lower and higher depression levels, respectively. This study confirms the importance of daily life experience in the development of psychopathology. By identifying significant associations between life events and depression, this research offers potential avenues for tailored therapeutic approaches and improved mental health outcomes.

Neuroimaging studies that investigate the neural correlates of depression largely do not discern the difference between state-level depression and trait-level depression. State-level depression refers to short-term fluctuations in mood that are typically associated with changes in an individual’s environment or circumstance. Whilst trait level depression is considered to be stable over time and reflects long-term individual differences in depression level; being indexed by the personality trait of neuroticism.
Such studies have used independent component analyses or seed-based correlation analyses to define networks. However, a newer technique, Probabilistic Functional Modes (PROFUMO) (Harrison et al., 2015) is a data decomposition method that adopts a hierarchical Bayesian model to optimize both group and subject estimates, simultaneously. PROFUMO was developed relatively recently and has not yet been tested in mental health population. The second aim of this thesis is to discern dissociable PROFUMO neural correlates of state versus trait depression using longitudinal and cross-sectional data. The findings revealed that functional connectivity was related to state depression, whereas spatial network organization was related to trait depression. In addition to association networks such as the default mode and salience network, state and trait depression were both associated with sensorimotor networks such as the visual and somatosensory networks. This study confirms the presence of differential neural correlates of state and trait depression and highlights the need to distinguish between the two in terms of informing biomarker usage for treatment tracking effects compared to identifying at-risk individuals. More so, the study highlights the need for further investigation into the role of sensorimotor networks in the onset of depression.

Research into the neural correlates of life events largely focuses on individual classes of events, such that the cumulative neural correlates of an experience of multiple hassles/uplifts are unknown. The third aim of this thesis is to identify the neural correlates of cumulative life events using PROFUMO and to determine whether they overlap with the neural correlates of depression using a conjunction analysis. The findings revealed that functional connectivity and network organization in a similar circuitry of association and sensorimotor networks were associated with life events, but there were no directly overlapping neural correlates between depression and life events. This study highlights the complex interplay between life events and brain function and has the potential to guide the development of interventions that target specific neural networks, thereby leading to enhanced efficacy and improved mental health outcomes.

Taken together, this thesis enhances our understanding of the cumulative impact of life events on depression and provides evidence for the differential PROFUMO neural correlates of state and trait depression. By identifying significant associations between specific life events, neural networks, and types of depression, this research provides
valuable insights for the development of targeted interventions aimed at improving mental health outcomes.
Chapter 1: Introduction

1.1. Context and Motivation

Depression is reported to be one of the leading causes of disability and poor health globally (WHO, 2017), with the lifetime risk of depression estimated to be between 15-18% (Bromet et al., 2011). Depression impacts a patient’s experience in terms of them living satisfied and fulfilling lives. Furthermore, patient’s contributions to society are in turn affected which impacts the labor economy with some studies reporting the average human capital lost per depressed worker being around $4426, which projects to $36.6 billion for the US labor force as a whole (Kessler et al., 2006).

There has been extensive research into the impact of traumatic events on depression. However, very little research has investigated the impact of daily life events – which are minor negative and positive events (such as falls in the last year and time spent outdoors, respectively) that people experience on a day-to-day basis – on an individual’s depression level. Similar to traumatic events, these daily life events may result in changes to mental health both cross-sectionally and longitudinally. Being able to identify which life events impact depression can enable economic and non-clinical targets to be identified to reduce or limit the onset of depression. The availability of population data, such as that seen in the UK Biobank dataset (Sudlow et al., 2015), now enables large-scale epidemiological investigations. The breadth of phenotypic measurements within the UK Biobank (in excess of 400 variables) enables the curation of a modern list of life events that can be used to investigate their relationship with depression.

In addition to behavioral changes, there is extensive research into depression being a network-based disorder impacting connectivity within a number of brain networks (see section 1.3 for details). Studies into network-based changes in depression rarely
distinguish between state- or trait-based depression. The UK biobank includes a range of depression measures and neuroimaging data available both cross-sectionally and longitudinally which enables the investigation into network-based neural correlates of state- or trait-based depression. To discern the neural correlates of depression, there are various ways to define brain networks however, an underutilized approach within the field – Probabilistic Functional Modes (PROFUMO) – will be focused upon, given its added advantage in terms of more accurately measuring individual differences in behavior and allowing for network overlap (Bijsterbosch et al., 2018). Moreover, the multitude of spatial and temporal PROFUMO outputs have been shown to be a key source of behaviorally relevant information (Bijsterbosch et al., 2018). Therefore, it is of interest to test the potential value of this method for identifying markers of mental health symptomatology. As PROFUMO was developed relatively recently and has not yet been tested in mental health population, the novelty of investigating if there are differential resting state brain networks implicated in different types of depression is an exciting prospect.

More so, previous research has also implicated several life events independently having an impact on depression levels. As such, one would expect changes in life events that impact depression may also be reflected in implicated resting state brain networks through changes in connectivity levels. However, research over the years has seldom investigated the additive impact of a large group of general life events on depression, and furthermore, their impact on networks implicated in depression. As such, the ability to access data on life events, depression, and neuroimaging within the UK Biobank allows for the ability to discern the neural correlates of life events and to assess if there is any overlap with the neural correlates of depression. If these correlates did exist, they would serve as potential biomarkers linking life events to depression. More so, if they did overlap, they would allow for life events to serve as an economical target as a means of possibly limiting the onset of depression. Taken together, this thesis aims to assess the impact of daily life events on depression symptomatology and discern their neural correlates within resting-state networks as deduced by PROFUMO.
1.2. **Background: Impact of life events & traumatic events on depression**

Due to the heterogeneity of an individual’s experience in their daily lives, it is important to note that a number of events take place. Some events can be traumatic in nature, and encompass scenarios such as physical or sexual abuse, natural disasters, or combat exposure. Others can be general life events that are less intense in nature such as a quarrel with a friend, work stress, and irritation from a health issue. Yet, both types of events can potentially contribute to the development of depression. Another type of general life event are those which are uplifting in nature, such as having the ability to confide in someone or enjoying a stroll outside. These events can be seen as potentially having the ability to counteract the development of depression. This section aims to assess the relationship between life events and depression, and the need to consider and control for traumatic events when investigating such a relationship with depression.

### 1.2.1. The relationship between life events (Hassles & Uplifts) and depression

General life events encompass daily occurrences one can experience. In 1981, Kanner and colleagues separated such general life events into two categories. The first group of events was coined Hassles, which were defined as “irritating, frustrating, distressing demands that to some degree characterize everyday transactions with the environment (Kanner et al., 1981).” Some examples of hassles include the length of a person’s commute to work and the presence of bodily pain. Daily hassling events, such as stress from work or personal relationships are reported to have an impact on an individual’s mental health and well-being (Woo & Postolache, 2008; Ishikawa, Kohara & Nushimoto, 2022; Törrönen et al., 2021). These events may not be as severe as traumatic events, but they may still contribute to the development of depression by overwhelming an individual’s coping mechanisms and contributing to feelings of hopelessness, helplessness, and despair. This idea of difficulties and strains impacting depression severity has been investigated by numerous scientists over the years, for example, Holmes and Rahe developed the SRRS: Social Readjustment Rating Scale (Holmes & Rahe, 1967) to assess the magnitude of different life events. The SRRS includes 43 hassling events each with a
Life Change Unit (LCU) that relates to the strain/hassle felt by their subjects. The LCU across the 43 life events were summed and used to determine a positive correlation with depression. In 1981, Kanner and colleagues decided to investigate daily hassles to discern whether a summed hassle score would be analogous to the LCU score from major life events, as per the SRSS. They found the hassles scale tended to be a more accurate predictor of stress-related problems when compared to the SRRS. More recently, daily hassles were found to have a higher correlation with adolescent behavior when compared to life events, with hassles related to family problems, issues in school, and self-perception being most predictive (Courtois et al., 2007).

The second group of general life events were termed Uplifts, which were defined as “events that make you feel good and are positive experiences (Kanner et al., 1981).” Some examples include time spent outdoors and having the ability to confide. Research into a group of uplifts impacting depression is sparse. Nevertheless, uplifting events, such as experiencing a positive social interaction and walking outside, can have a positive impact on an individual’s mental health and well-being; these events can improve mood and reduce symptoms of depression by increasing feelings of happiness, hope, and self-worth (Folkman & Moskowitz, 2000; Maybery et al., 2006; Kun & Gadanecz, 2022). However, during the study by Kanner and colleagues in 1981, they were able to show both hassles and uplifts were distinct descriptors of life stress in divergent populations and individuals, as state variables subject to change, and as possible mediators of the effect on adaptational outcomes of life event. Specifically, they found that the effect of major life events on depression experienced by a person were partially mediated by the degree and frequency of daily hassles and uplifts they experienced. This suggests that the experience of daily hassles and uplifts may help to explain why some individuals are more resilient in the face of major life stressors than others. To assess the impact of life events on depression, in Chapter 2, similar to the LCU, a cumulative score for each life event is developed following the binarization of their response scales (see Chapter 2, Section 2.4 for more details).
1.2.2. Considerations of the impact of traumatic events and depression

Despite the sparse research into the impact of life events on depression, there is extensive prior work on the impact of traumatic events on depression. Trauma, as per the DSM-V (American Psychiatric Association., 2013) requires “actual or threatened death, serious injury, or sexual violence.” Some examples of traumatic events include experiencing assault, accidents, or a natural disaster. This differs from hassling life events as they do not involve serious threats to life or physical injuries such as psychosocial hassles (non-traumatic life events e.g., job loss), and are not encompassed in this definition of trauma. Several studies have reported exposure to traumatic events being associated with an increased risk of developing depression. The meta-analysis conducted by Rubens, Felix & Hambrick, in 2018 examined the impact of natural disasters on the mental health of children and found those who were exposed to natural disasters were at increased risk of developing depression and other mental health problems. Another systematic review of a group of refugees found that exposure to traumatic events was associated with an increased risk of developing depression (Steel et al., 2009). Similar results were reported in veterans exposed to traumatic events during military service, which was associated with an increased risk of developing depression (Sherman et al., 2015). Importantly, prior work has also shown that individuals who have experienced traumatic events tend to suffer from more daily hassles than those who have not experienced traumatic events (Stensvehagen et al., 2022). Therefore, it is an open question as to whether the association between hassles and depression exists independently of traumatic events or whether it is fully explained by traumatic events. In Chapter 2, I will address this question by determining the relationship between cumulative life events (hassles and uplifts) and depression.

1.3. Background: Neural correlates of depression

Given the availability of imaging techniques, research into the neural correlates of depression have looked at brain regions that correlate well with established biomarkers of depression or functional networks implicated in depression (Li et al., 2021). Despite such studies, the neural mechanisms underlying depression remain poorly understood.
This section provides a review of the background on the resting state functional magnetic resonance imaging (rs-fMRI) neural correlates of depression and highlights brain changes observed in these studies at a network level along with the difference between state and trait depression. The section concludes with a review of the techniques used to define rs-fMRI brain networks, which are crucial for understanding the neural basis of depression.

### 1.3.1. Brain changes in rs-fMRI studies of depression

Rs-fMRI examines the level of co-activation between the functional timeseries of anatomically separated brain regions during rest and is thought to be suitable for studying depression as it provides a way to investigate connectivity between different regions and networks in the brain. Functional connectivity refers to similarities in patterns of brain activity between regions within the brain, where two regions are said to be functionally connected if the timeseries of their activity is highly correlated. Over the past decade, rs-fMRI studies have reported abnormal connectivity levels in depressed subjects both within and between networks (Greicius et al., 2007; Yu et al., 2019). The default mode network (DMN) is a network of brain regions that is active during rest and is thought to be involved in self-referential processing and mental stimulation. Several studies have reported increased DMN connectivity in individuals with depression compared to healthy controls, particularly in the posterior cingulate cortex and the medial prefrontal cortex (Mulders et al., 2015; Posner et al., 2015; Yu et al, 2019). The increased connectivity within the DMN in depression is thought to be related to rumination, negative self-referential processing, and impaired attentional control.

Another network that has been implicated in depression is the salience network (SN). The SN is involved in detecting and filtering salient sensory, emotional, and cognitive information and is thought to play a role in modulating the activity of other networks. Several studies have reported altered connectivity patterns within the SN in individuals with depression compared to healthy controls, particularly in the insula and dorsal anterior cingulate cortex (Mulder et al., 2015; Kandilarova et al., 2018; Yu et al, 2019). There is evidence of a link between the alterations in SN connectivity in depression being
linked to altered emotional and cognitive processing as seen in Sheline et al., 2009 which reported increased activity within the network during a task involved in self-referential processing. A later meta-analysis by Kaiser et al. (2015) found that depressed patients exhibited decreased connectivity within the SN which was associated with increased negative processing and decreased cognitive control.

A number of studies have reported alterations in connectivity between networks implicated in depression in addition to alterations within individual networks. In 2015, Mulder and colleagues conducted a review of rs-fMRI studies into depression and proposed a model that incorporates changes in functional connectivity within current hypotheses of network dysfunction in extreme depression. They reported four consistent findings in changes in network connectivity that were noted in relation to the resting state networks. The first finding indicated a decreased connectivity between the SN and DMN in individuals with depression compared to healthy controls, particularly in the dorsal anterior cingulate cortex, a key region of the SN, and the posterior cingulate cortex (PCC), a key region of the DMN. This decreased connectivity between the SN and DMN has been linked to deficits in attentional control and cognitive processing in depression, as well as alterations in emotional and cognitive processing (Lu et al, 2015).

The review by Mulder et al., (2015) also reported three other findings related to altered connectivity in depression. The second finding reported increased connectivity in the anterior DMN, including the medial prefrontal cortex and anterior cingulate cortex, in patients with major depressive disorder compared to healthy controls. These findings suggest that different regions of DMN connectivity may be altered in depression, with implications for self-referential processing and emotion regulation (Sheline et al. 2009). The third finding was altered connectivity between the anterior and posterior DMN, particularly in the PCC, and increased effective connectivity from the ventral anterior cingulate cortex to the PCC. This example of altered effective connectivity was associated with higher levels of anhedonia, a core symptom of depression characterized by the inability to experience pleasure (Sheline et al., 2009; Geller, Liu & Warren, et al., 2017). Lastly, Mulder and colleagues reported decreased connectivity between the DMN and the frontoparietal network (FPN), a network that is involved in attentional control and cognitive processing. More so, this decreased DMN-FPN connectivity has been linked to
deficits in attentional control and cognitive processing in depression (Kaiser et al., 2015; Mulder et al., 2015).

Although the findings from rs-fMRI studies have provided valuable insights into the neural mechanisms underlying depression (Mulder et al., 2015; Yu et al., 2019) there are several inconsistencies in the literature that needs to be addressed. In a meta-analysis conducted by Tozzi et al. 2021, reduced functional connectivity was reported in the DMN in depression which contrasts with Zhang et al. (2019) who reported increased connectivity in the anterior DMN. However, a meta-analysis by Saberi et al. (2021) found no significant findings regarding functional alterations between the SN and DMN. The inconsistencies reported within the literature highlight the need for rigorous and standardized methodologies when conducting rs-fMRI depression studies. Therefore, despite connectivity within and between the SN & DMN being implicated in depression, the precise nature of this connectivity is still being explored, and further research is needed to clarify the underlying mechanisms. In Chapter 3, I will address this question by determining the resting state correlates of state and trait depression.

1.3.2. What is the difference between state & trait depression?

When reviewing studies into network-based changes in depression, it is unclear whether these studies are investigating markers of state or trait depression. State depression refers to the current symptoms one experiences – being temporary in nature – with short-term fluctuations in depression levels that are more responsive to changes in the individual’s environment or circumstance (Chiappelli et al., 2014). State-level depression can be triggered by specific events or situations (e.g., daily hassles), which can contribute to the development and maintenance of depression. Whereas trait-level depression reflects the general tendency to experience depression across the lifetime – being more stable in nature – and contributes to long-term individual differences in depression levels (Chiappelli et al., 2014). Trait-level depression can be measured as the personality trait of neuroticism, which is characterized by a tendency to experience negative emotions such as anxiety and sadness (Klein, Kotov & Bufferd., 2011), and is regularly seen as a substitute in studies investigating depression. This approach was seen in a previous study based on the dimensional view of depression, in which the experience of clinical and subclinical levels of depressive symptoms over time was
reported to reflect an enduring phenotype; which may be related to the disposition to clinically defined depressive illness (Chiappelli et al., 2014).

Importantly, studies rarely make a distinction between state and trait depression due to the high correlation between the two types of depression in cross-sectional studies being reported as greater than 0.6 (Ormel et al., 2004; Bagby et al., 2008; Kotov et al., 2010). This is compounded by the fact that state and trait depression are not completely independent constructs and that one can influence the other. For example, a person with high levels of trait depression is more likely to experience state depression. It is also worth noting that while state and trait depression are related, they are also distinct constructs, and as such, it is important to differentiate between them in order to understand whether there are distinct network-based changes associated with state and trait depression. One option to dissociate the highly correlated constructs of state and trait depression is to perform a longitudinal study with individuals who have a large change in their depressive symptoms. In Chapter 3, such a longitudinal approach is taken to identify differential neural correlates of state and trait depression.

1.3.3. Techniques to define brain networks

There are several resting-state methods that can be used to define networks. The first includes seed-based correlation analysis (SCA), which involves selecting a seed region of interest (ROI) and correlating each voxel timeseries with that of the pre-selected seed ROI to estimate the correlation of all gray-matter with the seed. SCA is a simple and widely used method, but it is limited by the choice of seed ROI and may not fully capture the complexity of functional connectivity in the brain. Seed-based approaches are sensitive to changes in the connectivity of the seed region under investigation, this high sensitivity can lead to spurious findings with no biological meaning (Power et al., 2017). The second method, independent component analysis (ICA) is a data-driven decomposition method used to parcellate the brain into resting state networks, which is combined with dual regression to extract subject-specific spatial network timeseries used to estimate correlation-based network matrices and network amplitudes. More specifically, ICA decomposes the fMRI data into functional networks based on their similarity and temporal coherence. ICA is a powerful method that can uncover network patterns of brain activity (Beckmann et al., 2015). An alternative to ICA and dual
regression is Probabilistic Functional Modes (PROFUMO) (Harrison et al., 2015). PROFUMO is a data decomposition method that adopts a hierarchical Bayesian model to iteratively optimize subject and group estimates, which makes this method more likely to capture subject-specific spatial variability more accurately than dual regression. There are various considerations when deciding which measures to use as seen in Table 1.

**Table 1 Consideration for resting-state derived measures (SCA, ICA & PROFUMO)**

<table>
<thead>
<tr>
<th>Resting-state derived measures</th>
<th>Considerations</th>
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| Seed-based correlation analysis (SCA)             | ▪ It is straightforward to implement and intuitive to interpret.  
▪ Seed-based approaches are very sensitive to changes in the connectivity of the seed region under investigation.                                      |
| Independent component analysis (ICA)              | ▪ ICA provides a multivariate decomposition into many components that together best describe the full dataset.  
▪ The split between networks is sensitive to the dimensionality (set by the researcher), noise characteristics, and psychopathology. This can complicate the interpretation of results in relation to the existing literature.  
▪ To circumvent this sensitivity to dimensionality in clinical research, template ICA components can be used, instead of taking a data-driven approach to obtain study-specific networks, but the downside of this approach is that the resulting network structure may not capture the data well. |
| Probabilistic functional modes (PROFUMO)          | ▪ PROFUMO can disentangle sets of modes with complex spatiotemporal interactions and infer information about the nature of variations across subjects.  
▪ PROFUMO has been most strongly linked to individual differences in behavior in healthy subjects. |

Recent findings have indicated that spatial information derived from PROFUMO was most strongly linked to individual differences in behavior in healthy subjects (Bijsterbosch et al., 2018). As PROFUMO was developed relatively recently and has not yet been tested in mental health populations. Therefore, it is of interest to test the potential value of this method for identifying markers of mental health symptomatology, specifically in relation to depression.
1.3.4. Probabilistic Functional Modes: PROFUMO

The PROFUMO algorithm uses a matrix factorization model that decomposes data into estimates of subject-specific spatial maps, time courses, and amplitudes (which, together are known as a mode). This is done by using a variational Bayesian approach with both spatial priors (for map sparsity and group map regularization) and temporal priors (consistent with the hemodynamic response function [HRF]) (Bijsterbosch et al., 2019; Harrison et al., 2015) that seek to optimize for both spatial map sparsity and temporal dynamics consistent with hemodynamically regularized neural activity. PROFUMO simultaneously estimates subject and group probabilistic functional mode maps and network matrices. A PROFUMO mode in a mathematical sense is the outer product of a spatial map and a time course, constrained by the nature of both the between-subject variation and the effect of the hemodynamic response function. This is presented as a probabilistic generative model within a variational framework that allows Bayesian inference, even on voxelwise rs-fMRI data. This approach allows one to infer distinct extended modes that are correlated with each other in space and time, a property that has been said to be neuroscientifically desirable (Harrison et al., 2015). When compared with ICA, PROFUMO is seen to stably infer sets of modes with complex spatiotemporal interactions and spatial differences between subjects. As well as being derived at the group level, a mode can also be derived at a subject level across a whole cohort simultaneously, it is also described by a subject-specific spatial map and a set of time courses.

The hierarchical approach that PROFUMO adopts is done by iteratively optimizing subject and group estimates instead of first estimating group components using group ICA and separately mapping these onto subjects using dual regression. Due to this, PROFUMO is expected to capture subject-specific spatial variability more accurately than dual regression. PROFUMO integrates a multitude of rs-fMRI data properties using the PROFUMO framework. In the spatial domain, it adopts a sophisticated group-level model that encompasses both mean effects and typical patterns of variability. This model allows for the standardization of subject-specific spatial maps. The temporal model is based on the physiological properties of the blood oxygen level dependent (BOLD) signal and includes a hierarchical model to illustrate the functional coupling between modes.
PROFUMO also accounts for differences in overall activity levels of modes using the amplitude parameters. It is also possible to produce further summaries by combining parameters, including measures related to the fractional amplitudes of the BOLD signal.

The probabilistic functional mode maps obtained from PROFUMO commonly show extensive amounts of spatial overlap (and hence spatial correlation) between modes. These overlapping regions may contain a spatial representation of complex between-node patterns of functional connectivity. In Bijsterbosch et al. (2019), the authors found that PROFUMO networks showed significant overlap with each other, which could reflect the presence of intermediate regions that are involved in multiple functional networks. Therefore, it is of interest to test the potential value of this method for identifying markers of mental health symptomatology. As PROFUMO was developed relatively recently it has not yet been tested in mental health populations and studies investigating the neural correlates of depression and life events in Chapter 3 and 4 will utilize resting state measures obtained using PROFUMO.

1.3.5. PROFUMO outputs: Amps, NetMats, Spatial Overlap

To discern the neural correlates of state & trait depression PROFUMO will be utilized to define brain networks. Although it shares similarities with ICA, it also has the added advantages in terms of more accurately measuring individual differences and allowing for network overlap. PROFUMO decomposes rs-fMRI data into a set of modes, where each mode is described by a spatial map, amplitude, and timeseries (as seen in Figure 1) which can be derived at the group and subject level, for more details see Chapter 3, Section 1.4. For this thesis, three PROFUMO outputs were used: amplitudes – which indicate the networks strength, network matrix – which indicate the temporal connectivity between a pair of networks using the timeseries of the mode, and spatial overlap matrix which looks at the degree of similarity between two probabilistic maps.
Figure 1. A PROFUMO mode encompasses spatial maps, amplitudes, and timeseries. Spatial maps indicate the spatial layout of a mode. They can be used to derive the spatial overlap matrix between two spatial maps of a mode to indicate the degree of similarity. The amplitude of a mode is the network strength. The network matrix is the correlation between the timeseries of two networks.

**AMPs: Amplitudes**

Amplitudes reflect the strength or intensity of a resting state network. PROFUMO amplitudes are estimated as a scalar weight during decomposition. The amplitude is influenced by a variety of factors, including the strength of the neural response, the level of noise in the measurement, and the physiological properties of the vasculature and hemodynamic response.

**NetMats: Network Matrices**

Netmats are a mathematical concept used in the analysis of functional connectivity in neuroimaging studies. They are a matrix representation of pairwise functional connections between a pair of networks in the brain, where each entry in the matrix represents the strength of the connection between two networks. As such, netmats can be used to study individual differences in functional connectivity, by comparing the strength and pattern of connections between different individuals or groups. This can provide insights into the neural basis of individual variability in cognitive and behavioral processes.
Spatial Overlap Matrix

Spatial maps represent the spatial distribution of each network in the brain. PROFUMO uses a weighted decompositions rather than binary parcellations and is based on the spatial similarity of the voxel to the independent components, providing a more fine-grained characterization of the brain’s functional organization. Using these maps one can calculate the spatial overlap matrix which represents the degree of similarity or overlap between different spatial maps of networks (as seen in Figure 1). The spatial overlap matrix is then calculated by computing the spatial correlation between all pairs of spatial maps. The spatial overlap matrix can be used to study individual differences in the organization of large-scale functional networks. Thus, the spatial overlap matrix provides a powerful tool for understanding the structure and function of the brain.

1.4. Background: Overlapping correlates of life events and depression

A hypothesis can be put forward that life events such as hassling events may contribute to feelings of hopelessness, helplessness, and a lack of control over one’s life that can result in the onset of depression. Furthermore, uplifting events may equip individuals with mechanisms to cope with stressful life events and prevent the development of depression. However, research into the additive effect of a group of life events and their brain correlates is limited, thus research into the overlapping brain correlates of life events and depression is sparse. This section provides a background on the rs-fMRI neural correlates of life events, alongside referring to more researched bodies of literature (such as neural correlates of traumatic events). The section concludes by drawing parallels between the allostatic load model of depression and its impact on physiological systems including the brain, which provide a psychological explanation for the existence of possible overlapping correlates of life events and hassles.

1.4.1. Brain changes in rs-fMRI studies of life events.

Studies into the neural correlates of specific classes of hassles are limited, and to date, only 2 studies have explicitly investigated this topic. (Mulligan et al., 2022; Butterworth
et al., 2011). Despite the lack of research into the resting state neural correlates of hassles, research has shown that depressed individuals have a stronger memory for negative occurrences, with more activity in their amygdala (Ramel et al., 2007; Hamilton & Gotlib, 2008). However, there is a lack of work on the network-based neural correlates of the cumulative impact of suffering from a range of hassles. When considering uplifts, physical activity levels are a consistent group of uplifts that are studied, where research has shown that connectivity strength and amplitude of the DMN, SN, and Central Executive Network (CEN, a component within the FPN) were associated with mental health and physical activity (Zhang et al., 2022). Studies into subjective well-being have also shown weaker connections between the SN and anterior DMN, as well as the DMN and FPN (Shi et al., 2018) indicative of more flexibility and adaptivity in rs-fMRI networks involved in self-reflection, emotional regulations, and cognitive control. It should be noted that those with depression do exhibit with symptoms that include a loss of interest in activity and pleasure; and most uplifting events are as a result implicated and thus their effect reduced. Taken together, these examples indicate increased activity within DMN, SN, FPN, and CEN, which may have a protective effect against hassling events and depression.

However, research has also shown greater connectivity in the DMN during self-referential processing in response to negative emotional stimuli compared to neutral stimuli (Sheline et al., 2009; Wagner et al., 2015). More so, the SN has also exhibited lower connectivity and fewer connections within the network for those who experience higher levels of positive feelings (Qi et al., 2021). The FPN is positively correlated with the propensity to subdue negative sentiments (Pan et al., 2018) but it is not solely determined by the emotional valence of the stimuli and has been seen to be activated during working memory tasks (Braunlich, Gomez-Lavin, Seger, 2016). Nonetheless, research as a whole into the resting state neural correlates of a group of hassles and uplifts is lacking particularly from a network-based approach, and warrants further research. In Chapter 4, the same resting state measures obtained using PROFUMO in Chapter 3 will be used to investigate the neural correlates of life events.
1.4.2. The impact of life events and depression on the brain: allostatic load model.

The allostatic load model of depression states that the cumulative burden of chronic stress and life events will impact physiological systems, including the brain (see Figure 2). As such, when the brain perceives an event as stressful this initiates physiologic and behavioral responses which lead to allostasis and subsequent adaptation. Stress exposure – which can be defined as the perception of exposure to a threat – offsets these very mechanisms that initiates the allostatic responses. One can think of the concept of allostasia as the body’s adaptation to stressors (i.e., hassling events).

![Figure 2. The central role of the brain in allostasis and the behavioral and physiological response to stressors (From McEwen, 1998)](image)

In the context of brain systems, allostasis can be thought of as the wear and tear that accumulates due to the prolonged periods of stress and strain (McEwen, 1998). As the brain works to maintain its homeostasis in face of the exposure to such allostatic loads, this increases the brain’s vulnerabilities to a range of disorders including depression (McEwen, 2000; McEwen & Akil, 2020). This is analogous to the notion of life events causing stress to the point of illness (depression) as seen by Meyer in his life work chart (Meyer, 1919); which then became the foundation of the Schedule of Recent Events (Hawkins, Davies & Holmes, 1957) that investigated the cumulative effect of life events in causing stress and illness. Therefore, it is expected that the neural correlates of hassles
will overlap with the neural correlates of depression. As such, research is warranted into whether there are overlapping neural correlates of life events and depression. In Chapter 4, this question is addressed by determining if there are any overlapping functional brain networks between depression and life events (hassles and uplifts).

1.5. **Background: Importance of large-scale epidemiological studies.**

When assessing studies into the neural correlates of depression they are all challenged by their small sample sizes. Despite progression from research on a couple of dozen participants to those in the mid-fifties with the occasional studies comprising of over a hundred participants, issues still persevere. This is primarily because acquiring neuroimaging data is expensive when compared to other modalities. The prevalence of small sample sizes in the field of Neuroscience (Button et al., 2013) is reflective of a low statistical power such that results are unlikely to be reflective of a true effect. Moreover, the low number of subjects results in high sampling variability such that replicability becomes an issue (Poldrack et al., 2017, Marek et al., 2020).

However, the initiation of big datasets enables the field to address the current challenges surrounding heterogeneity, biomarker variability, identifying the optimal markers, and bringing the field toward translational, applied research in depression. The health sciences have only recently begun using big data analytics, a decade or so later than the business sector (Dash et al., 2019). However, studies such as iSPOT-D and consortia such as the Psychiatric Genetics Consortium are progressing our understanding of biological mechanisms in Psychiatry (Arnow et al., 2015; Consortium, 2013). In a few studies, machine-learning algorithms have been applied to investigate biomarkers for depression such as in Dipnall et al., 2016, where they used a dataset of 5000 participants, with multiple imputation steps and a machine-learning boosted regression to discern 21 potential biomarkers.

When assessing neuroimaging datasets, they span in size from the Human Connectome Project (Van Essen et al., 2013) which encompasses 1,200 participants, Adolescent brain Cognitive Development (Marek, 2020) which is 10 times larger (n=11,878), and the largest of them all, the UK Biobank (Sudlow et al., 2015) which currently hold
neuroimaging data on 45,000 individuals (upon study completing data will be available on 100,000 subjects). More so, large-scale samples ensure replicable results in the presence of low effect sizes (Marek et al., 2020). Marek and colleagues demonstrated how sampling variability alone was able to account for a broad range of observed brain-wide associations particularly inflated correlations. When considering the statistical power afforded by these datasets, one can place greater confidence in the idea that studies using such large datasets will produce a result that indicates a true effect. The studies mentioned in Chapter 2, 3 and 4 will utilize the UK Biobank dataset.

1.5.1. UK Biobank Data Collection

UK Biobank is a prospective cohort study of over 500,000 individuals from across the United Kingdom. Participants, aged between 40 and 69 at the time of recruitment, were invited to one of 22 data collection centers across the UK between 2006 and 2010 for their initial consent and assessment (‘instance 0’). Neuroimaging data acquisition started in 2014 (‘instance 2’). There were three identical neuroimaging sites across England which included identical scanners: standard Siemens Skyra 3T with a standard Siemens 32-channel RF receive head coil. The Echo-Planar Imaging (EPI) based acquisitions for resting state fMRI utilized simultaneous multi-slice (multiband) acceleration (Larkman et al., 2001, Moeller et al., 2010). For resting-state fMRI resolution utilized was 2.4x2.4x2.4 mm, with a field-of-view of 88x88x64 matrix and anterior-posterior phase encoding. The duration of each scan was 6 minutes (490 timepoints) with a TR of 0.735 seconds, a TE of 39 milliseconds, a GE-EPI with x8 multislice acceleration, no iPAT, a flip angle of 52°, and fat saturation. Acquisition for all other sequences are available in Table 1 of Alfaro-Almagro et al., 2018. As implemented in the CMRR multiband acquisition, a separate single-band reference scan was also acquired. This has the same geometry as the timeseries data, but has higher between-tissue contrast to noise, and is used as the reference scan in head motion correction and alignment to other modalities.

1.5.2. Quality control

A rigorous quality control process was implemented to ensure the reliability and consistency of the brain imaging data shared by the UK Biobank (Alfaro-Almagro et al., 2018). The purpose of this quality control procedure was to identify and address any potential issues or
artifacts that could compromise the integrity of the data. A supervised machine learning ensemble classifier was trained to label all UK Biobank T1-weighted images as ‘problematic’, ‘imperfect’, and ‘good’ based on 190 quality control features (Alfaro-Almagro et al., 2018). Training data consistent of 5816 manually labeled UKB participants, out of which problems were identified in 103 participants. The trained algorithm is applied to all subsequent UKB participants to flag potentially problematic datasets for manual inspection. Datasets deemed unusable are not shared with UKB users and are therefore automatically excluded from all studies in this thesis.

1.5.3. Preprocessing pipeline

The data is corrected for motion artifacts using MCFLIRT, a motion correction algorithm (Jenkinson et al., 2002). This step aligns each volume in the time series to a reference volume to compensate for head motion during data acquisition. Next grand-mean intensity normalization was applied on the entire 4D [time, space (x,y,z)] dataset by using a single multiplicative factor (usually 10,000) to ensure consistent intensity across the volumes. Thereafter, a high-pass temporal filtering (with a cut-off of 50s) was applied to the data to remove the low-frequency drifts. Distortion correction of EPI requires an estimate of the static field map. This fieldmap is derived from pairs of spin-echo EPI acquisitions with opposite phase encoding directions, 3 b=0 images are acquired with reversed phase encoding for later fieldmap estimation (along with 3 b=0 images with standard phase encoding). The estimated fieldmap is used for distortion correction in fMRI datasets to correct geometric distortions caused by magnetic field inhomogeneities (e.g., air-tissue boundaries). Thereafter, the data was nonlinearly warped to MNI152 space using FNIRT (FMRIB’s Nonlinear Image Registration Tool (Andersson et al., 2007b, Andersson et al., 2007). Lastly, independent component analysis and was used to separate the fMRI data into spatially independent components, and FIX removed components related to noise sources, such as motion or physiological artifacts (Beckmann and Smith, 2004; Salimi-Khorshidi et al., 2014; Griffanti et al., 2014). FIX was trained on 40 Biobank rfMRI datasets and achieved high accuracy in classifying artifact and non-artifact components. All imaging data utilized in this study was preprocessed via the aforementioned pipeline by the Wellcome Centre for Integrative Neuroimaging at Oxford University, and preprocessed data were shared through the UK Biobank showcase.
1.5.4. Advantages of the UK Biobank dataset

Outside of the neuroimaging data on the 45,000 individuals, the UK Biobank dataset includes a wide range of information about the health and lifestyle of over 500,000 participants, including demographics, medical history, physical measurements, blood samples, and cognitive tests. It also includes self-reported information on mood, stress, and life events as well as neuroimaging data. The biggest benefit when using the UK Biobank is that its sample size allows for studies to be sufficiently powered, enabling them to improve the ability to detect small effects and reduce the risk of false negatives. More so, the wide range of data available in the UK Biobank allows researchers to control for potential confounders such as age, gender, medical history, and lifestyle – which can affect the results of any study. As such, due to the variety of variables and size of the dataset the UK Biobank enables the selection of general life events an individual experiences (needed for the study described in Chapter 2). Furthermore, the UK Biobank recruited a cohort of 500,000 participants, of which 100,000 subjects undergo one round of scanning and 10,000 of those subjects go through a second round of scanning (Sudlow et al., 2015) – a large enough sample to discern the neural correlates of life events and depression. At present, neuroimaging data is available on 45,000 subjects at timepoint 1 and 4,000 at timepoint 2. The collection of neuroimaging data at several timepoints over several years allows for researchers to conduct both cross-sectional and longitudinal studies (important requirements to answer the overarching research question detailed in Chapter 3– see Chapter 3, Section 1.2 for more details). Taken together, the data encompassed within the UK Biobank is most suited to assessing the impact of daily life events on depression symptomatology and the neural correlates of state & trait depression.

1.6. Structure of Dissertation

Chapter 2 reviews the mapping process of modern-day life events within the UK Biobank dataset and the hassles and uplifts scale (Kanner et al., 1981). To study depression at the time of neuroimaging a continuous depression scale within the UK Biobank was developed – the need for its curations is explained in Chapter 2, Section 2.2. This first half of the chapter will provide details on a study that assesses the relationship between life events and depression through describing details on the dataset used, variable
selection criteria, curation of a depression measures and statistical models utilized. The second half of the chapter will showcase results on how life events are related to depression (before and after controlling for trauma), interaction effects, as well as which life events have the greatest contributions to an individual’s depression level and the significance of these results.

Chapter 3 reviews network-based rs-fMRI studies into depression and highlights the need to dissociate state and trait-level depression. To study network-based correlates of depression, the rs-fMRI technique of PROFUMO will be described along with the various PROFUMO output that can be utilized as potential correlates. This first half of the chapter will provide details on a study that investigates the network-based PROFUMO correlates of depression by describing details about the dataset used, discerning the ideal dimension for PROFUMO and the statistical models utilized. The second half of the chapter will showcase results on the optimal dimensions for running PROFUMO, the neural correlates involved in state & trait depression, and the significance of these results.

Chapter 4 reviews studies into network-based changes in rs-fMRI studies of life events and the motivation for how hassles could lead to an increase in depression through reviewing the distress-continuum, disorder-threshold model of depression (Wahid et al., 2021). The first half of the chapter will provide details on a study that investigates if there is an overlap in the PROFUMO correlates of life events and depression by describing details about the dataset used and the statistical models developed for discerning the neural correlates of life events. The second half of the chapter will showcase results on the PROFUMO correlates of life events and whether there are any overlapping correlates with depression (as discerned in Chapter 3), alongside the significance of these results.
Chapter 2: What is the relationship between life events and depression?

Studies into the impact of specific hassling and uplifting life events consistently report changes in an individual's depression level (Steger & Kashdan, 2009). However, few studies have investigated the impact of cumulative daily hassles or uplifts on depression. This chapter details a study that investigates the relationship between such life events and depression; after controlling for the effect of traumatic events given that previous studies have shown that traumatic life events can significantly impact depression levels. By controlling for traumatic events, the study aims to provide a more accurate understanding of the impact of daily life events on depression, and to identify which specific life events have the greatest contribution to an individual's depression level. The chapter begins by detailing the mapping of life events within the UK Biobank using a pre-existing framework (Kanner et al., 1998), as well as the need for a continuous depression measure (Recent Depression Symptom scale: RDS-4). This is followed by details of the methodology used and the subsequent results and their significance.

2.1. Background and motivation

Research has shown that both hassles and uplifts are distinct descriptors of life stress in divergent populations and individuals, as state variables subject to change, and as possible mediators of the effect on adaptational outcomes of life events (Bolger et al., 1989; Folkman & Lazarus, 1989; Kanner et al., 1981). Hassling events related to stress from work and personal relationships are reported to have an impact on an individual’s mental health and well-being (Muller et al., 2004; Stansfield et al., 1997). Whilst uplifting events are reported to possibly have a protective effect against depression by positively
impacting an individual’s mental health and well-being (Kashdan et al., 2014; Tugade & Fredrickson, 2007). The lack of research into a group of life events and their impact on depression motivates the need for such research to assess their overall effect on depression along with their independent contributions (Hammen, 2005). Due to established links between depression and traumatic events, it is important to control for this effect when investigating the relationship between life events and depression (Breslau et al., 1998; Kessler et al., 1995). By controlling for traumatic events, the results obtained would not be due to the influence of trauma and thus one can have confidence that results indicate a clear relationship between life events and depression. This study aims to investigate this relationship between life events and depression and hypothesizes that uplifts such as social support and physical activity will correlate with low depression scores as measured by the RDS-4, whilst hassles such as health conditions will be correlated with a higher depression score as measured by the RDS-4.

2.1.1. The Hassles Scale and Uplifts Scale (Kanner et al., 1981)

Kanner and colleagues developed two separate scales to assess the impact of life events on an individual. These life events were termed Hassles, which were defined as “irritating, frustrating, distressing demands that to some degree characterize everyday transactions with the environment,” and Uplifts which were defined as “events that make you feel good and are positive experiences.” Subsequently, this resulted in the development of the Hassle Scale which included 117 daily hassling events, and The Uplift Scale which included 135 daily uplifting events. These scales recorded the frequency (summed count; hassle range: 0-117, uplift range: 0-135), cumulated severity (summed 3-point severity rating; hassle range: 0-351, uplift range: 0-405), and intensity (cumulated severity divided by the frequency; hassle & uplift range: 0-3) of hassle & uplifts experienced in the past month (Kanner et al., 1981).

During their study, Kanner and colleagues found the hassles scale tended to be a more accurate predictor of state-level depression when compared to other scales such as the SRRS (which includes 43 stressful life events), whilst uplifts had a positive effect on the state levels. There was an attempt to assess the impact of daily events on mental health, with a revised combined Hassle and Uplift scale which focused on 8 factors (household,
financial, work, environmental, home maintenance, health, personal life, and family & friends) excluding health-related items, where everyday stress was associated with subsequent depression, mean levels of daily mood and overall health status (DeLongis, 1985). However, this scale only considered 53 overarching events which were ambiguous in terms of being hassles or uplifts.

Another attempt was seen through the development of a scale to assess hassles exclusively for depression: the Unpleasant Events Schedule (UES) which consists of 320 events across 7 rational scales: Health and Welfare, Achievement-Academic-Job, Domestic Inconveniences, Sex-Marital-Friendship, Material Financial, and Social Exits; where each event was rated for frequency of occurrence (3-point scale) during the past month and for subjective aversiveness (3-point scale) (Lewinsohn & Talkington, 1979). Despite the UES being able to differentiate between depressed and non-depressed individuals (Lewinsohn & Talkington, 1979) and the significant association between unpleasant events and depression level (Grosscup & Lewinsohn, 1980) there has not been widespread uptake by clinicians given how time-consuming it is (Lewinsohn et al., 1983). Additionally, similar to the Social Readjustment Rating Scale (SRRS) discussed in Chapter 1, Section 2.1 the UES encompasses major life events as well as hassles and excludes uplifts. Since then, only a few studies investigate the impact of hassles and uplifts in humans, where they have reported how hassles may have a cumulative effect on well-being over time (Almeida et al., 2011; Zautra, 2003) and uplifts have a positive effect on well-being in later life (Folkman & Moskowitz, 2000; Maybery et al., 2006). Thus, the Hassle Scale and the Uplift Scale (Kanner et al., 1981) will be mapped onto variables within the UK Biobank to curate a list of hassles and uplifts.

### 2.1.2. The relationship between life events (Hassles & Uplifts) and depression

This idea of difficulties and strains impacting depression severity was recently encapsulated in the distress-continuum, disorder-threshold model of depression (see Figure 3; Wahid et al., 2021) which used the general health questionnaire GHQ-12 (Sánchez-López & Dresch, 2008) to model minor psychological distress on a continuum between wellness and severely distressed.
Within this model, the symptoms of the GHQ-12 fall along a severity continuum across three derived classes: stress and strain, inability to face difficulties, and inability to make decisions. As such, these symptoms (seen in the blue portions of the bar chart, Figure 3) were the only areas of marked differences between the ‘distressed’ and ‘wellness’ classes; whilst traditional hallmark symptoms of anhedonia, depressed mood, and cognitive impairment only emerged for the severely distressed class (as seen in the orange portion of the bar chart, Figure 3), and were absent on the continuum otherwise. As such, this model indicates that if one aims to assess depression both cross-sectionally and longitudinally, it would be pertinent to focus on factors that increase difficulties and strain. Although this model does not map directly onto the research question investigating the relationship between life events and depression, it does provide support for the idea that stressful daily events such as hassles could accumulate over time to result in depression. Research has shown that people who have experienced more traumatic events may also experience more irritating daily hassling events, as trauma can affect an individual’s emotional and psychological well-being, and can make them more sensitive to stressors i.e., hassles. As such it is important to incorporate traumatic events from the lens of a confound to establish the relationship between life events and depression independently from traumatic events.
2.1.3. The need for a continuous depression scale

When considering the medical field, receiving a diagnosis is fundamental to accessing medical care. Such diagnoses have allowed for patients to gain access to medication, behavioral and financial support, proving to be a great help in comparison to those that are not diagnosed. However, when reviewing psychiatric diagnostic systems, they are almost entirely syndromic and categorical in nature, with some critics highlighting its development using inaccurate divisions centered on cross-sectional symptom groups that fail to discern the course of the illness variables themselves (Shahvaroughi, 2020; Clark et al., 2017). In depression, the use of a binary scale (e.g., seen in Figure 4) is said by some to limit medical care for those experiencing moderate symptoms as the categorical model relies on the symptom counts, such that 5 out of 9 symptoms are needed to meet the clinical criteria for diagnosis as seen in the Diagnostic and Statistical Manual of Mental Disorders published by the American Psychiatric Association. Despite such criticism, the current diagnostic system does perform well and has proven clinical utility.

![Binary Depression Scale](image1)

![Depression as a continuum](image2)

*Figure 4. A continuum of depression (adapted from Zoromba et al., 2015)*

Previous studies have reported how subsyndromal/subthreshold depression is linked to significant impairments comparable to those with suprathreshold depression (Gotlib, Lewinsohn, & Seeley, 1995; Judd et al., 1996; Sherbourne et al., 1994). Moreover, studies
have advocated for the use of depression severity as opposed to depression diagnosis being fundamental in forecasting subsequent impairment and outcome levels (Fergusson et al., 2005; Pickles et al., 2001). In 2011, Markon, Chmielewski & Miller reported an expected 15% increase in reliability and 37% increase in validity when a continuous scale of psychopathology was used in place of a discrete scale. Additionally, there is a growing body of research indicating depression to be continuously distributed along a continuum of severity in the general population (Patel, 2017; McGorry and Nelson, 2016). Following these findings, the National Institute of Mental Health proposed a dimensional approach across developmental trajectories and environmental effects to reconceptualize the processes underlying mental disorders (Figure 5: Clark et al., 2017).

Figure 5. A continuum of depression (from Clark et al., 2017) includes arousal and modulatory system, negative and positive valence, cognitive systems, and social processes.

However, clinicians cited issues with complexity and apparent lower clinical utility in diagnostic decision-making as a reason for low adoption rates (Patel et al., 2017).
Nonetheless, the continuum approach is increasingly being adopted within research into depression. In 2006, McGorry and colleagues highlighted the benefits of using clinical staging for psychiatric disorders as it not only provides a diagnosis but also details the extent of disease progression at the time of assessment. Consequently, this inherently provides a snapshot of where a person lies on the continuum of depression. Thus, within this study, a continuous depression scale was developed to account for those on the depression continuum.

### 2.2. Methods

#### 2.2.1. Dataset

From the total number of subjects in the UK Biobank (N = 502,444), after adjusting for dependencies, all subjects who did not have a continuous depression score (RDS-4; see Chapter 2, Section 2.2) were removed, and those who had life events data were retained which resulted in 19,829 individuals (out of which N = 10481 female; mean age = 54.85 ± 7.48). However, to factor in the confound of traumatic events, individuals who did not have such data were excluded, which resulted in 13,625 individuals (N = 7309 female, mean age = 54.97 ± 7.43) being retained for the purpose of this study.

#### 2.2.2. Curation of a continuous depression measure: RDS-4

The UK Biobank is host to different self-report measures which evaluate depression, these include Broad Depression (Howard et al., 2018) which assesses depression largely through whether help was sought; Patient Health Questionnaire (PHQ-9) (Kroenke et al., 2002) which assesses everyday depression through symptoms; Probable Major Depressive Disorder (Smith et al., 2013) which assesses clinical depression through symptoms and their duration as well as help sought. From the online mental health questionaries, Broad Depression presents a binary measure of depression that requires answering yes to one of two questions at either the initial or at any repeat assessment visit; or if there was a primary or secondary diagnosis of a depressive mood disorder from linked primary care and hospital inpatient data. Additionally, within the
questionaries, the PHQ-9 presents a continuous measure of depression that previous studies have used as a measure of depression (Levis et al., 2019).

Given the focus of depression on a continuum, the binary depression measures of Broad Depression and Probable Major Depressive Disorder were not suitable for this investigation. Additionally, although the PHQ-9 has a continuous response scale for each variable, it is obtained at a different time to the neuroimaging data acquisition which makes it not well-suited for neuroimaging research into depression within the UK Biobank—despite its validity for lifetime depression (Cannon et al., 2007), and its sensitivity to depression in older populations (Levis et al., 2019). Taken together, it was not the most optimum measure to investigate the overarching research question. Consequently, a new score was developed: the Recent Depressive Symptoms scale (RDS-4; Dutt et al., 2021) which encompasses variables from the assessment center (see Chapter 2, Section 2.3. which was also being used to identify hassles and uplifts) and was obtained on the day of brain scanning. The RDS-4 presents a continuous measure of state-level depression on the day of scanning with a rating scale from 1-4 for each of the 4 variables it incorporates as seen in Table 2, where the total sum ranged from 4-16.

Table 2 Indicates the variables selected from the assessment center and the rating scale for each variable used to discern the RDS-4 score.

<table>
<thead>
<tr>
<th>Assessment Center Code</th>
<th>Assessment Center Variable Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>2050</td>
<td>Frequency of depressed mood in last 2 weeks</td>
</tr>
<tr>
<td>2060</td>
<td>Frequency of unenthusiasm / disinterest in last 2 weeks</td>
</tr>
<tr>
<td>2070</td>
<td>Frequency of tenseness / restlessness in last 2 weeks</td>
</tr>
<tr>
<td>2080</td>
<td>Frequency of tiredness / lethargy in last 2 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rating scale for each variable</th>
<th>Question response for each variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Not at all</td>
</tr>
<tr>
<td>2</td>
<td>Several days</td>
</tr>
<tr>
<td>3</td>
<td>More than half the days</td>
</tr>
<tr>
<td>4</td>
<td>Nearly everyday</td>
</tr>
</tbody>
</table>

The selected variables for the RDS-4 incorporates a 2-week period which corresponds with the diagnostic criteria for depression as seen in the Diagnostic and Statistical Manual of Mental Health Fifth Edition (DSM-V: American Psychiatric Association, 2013). Moreover, the selected variables also incorporate the four domains considered in other depression measures including the Hamilton Depression Rating Scale (Hamilton, 1967)
and Montgomery-Åsberg Depression Rating Scale (Montgomery & Asberg, 1979). Furthermore, these questions in the RDS-4 correspond with the DSM-V diagnostic criteria for mental health, with the inclusion of the 2-week period time window (American Psychiatric Association, 2013). Taken together, the RDS-4 inventory is expected to reflect overall depression severity relatively well.

2.2.3. Curation of life events (Hassles & Uplifts)

The UK Biobank is the largest multimodal neuroimaging dataset which also encompasses data from questionnaires that pertain to everyday life. Given the breadth of non-specific questions asked to participants in the UK Biobank, this dataset allows for the application of stringent exclusion criteria for selecting variables that relate to general daily life events as seen in the Hassles & Uplift Scale (Kanner et al., 1981). When deciding upon suitable candidate variables which pertain to daily hassles and uplifts there are three sources of data within the UK Biobank which inform on mental health and associated factors. These include questions from the assessment center which participants complete via a touch screen on the day they were scanned. These questions relate to psychological factors, mental health, depression, self-reported happiness, satisfaction with health, family relationships, friendships, and financial situations. The second is a separately administered online mental health questionnaire which is completed by a subset of participants at a time independent of the scanning date. These questions were centered on mental distress, depression, mania, anxiety, addiction, alcohol use, cannabis use, psychotic experience, traumatic events, self-harm behaviors, happiness, and subjective well-being. The third, are health records which encompass the date of the first diagnoses as per the International Classification of Diseases Edition 10 (ICD-10) obtained from primary care and hospital inpatient data. These records covered clinical events, prescriptions, registration, carer support indicators, detention categories, detention date, history of psychiatric care on admissions, legal statuses, and mental health categories. Taken together, due to the variety of variables and size of the dataset, the UK Biobank ensures statistical power for the aims of the various research projects conducted within this thesis.
The UK Biobank Assessment Center had **8 main sub-categories** that were divided based on the type of assessment performed, this included: recruitment, touchscreen, verbal interview, physical measures, cognitive function, imaging, biological sampling, and procedural metrics. Due to the nature of the sub-categories, questions posed via the touchscreen were most appropriate as they encompassed questions on broad subject areas, including sociodemographic, lifestyle and environment, early life factors, family history, psychosocial factors, health & medical history, and sex-specific factors. From these 352 variables, 46 life events were identified variables that corresponded to questions from the Hassle Scale and the Uplift Scale as seen in Table 3. This resulted in the retention of 31 hassles and 15 uplifts.

*Table 3 Indicates the final list of life events: hassles (N=31) and uplifts (N=15) selected from the assessment center variables, with their respective codes.*

<table>
<thead>
<tr>
<th>UK Biobank Assessment Center</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hassle Code</strong></td>
</tr>
<tr>
<td>680</td>
</tr>
<tr>
<td>738</td>
</tr>
<tr>
<td>767</td>
</tr>
<tr>
<td>777</td>
</tr>
<tr>
<td>796</td>
</tr>
<tr>
<td>806</td>
</tr>
<tr>
<td>816</td>
</tr>
<tr>
<td>826</td>
</tr>
<tr>
<td>1090</td>
</tr>
<tr>
<td>1259</td>
</tr>
<tr>
<td>1558</td>
</tr>
<tr>
<td>2178</td>
</tr>
<tr>
<td>2188</td>
</tr>
<tr>
<td>2207</td>
</tr>
<tr>
<td>6148</td>
</tr>
<tr>
<td>2227</td>
</tr>
<tr>
<td>2247</td>
</tr>
<tr>
<td>2257</td>
</tr>
<tr>
<td>2296</td>
</tr>
<tr>
<td>2316</td>
</tr>
<tr>
<td>2335</td>
</tr>
</tbody>
</table>
2395 Hair/balding pattern               Categorical
2415 Had major operation              Binary
2844 Had other major operation        Binary
2463 Fractured/broken bones in last 5 years  Binary
2724 Had menopause female-specific factors  Categorical
6146 Attendance/ disability/ mobility allowance  Categorical
6149 Mouth/ teeth dental problems      Categorical
6159 Pain types experienced in the last month  Categorical
20107 Illnesses of father             Categorical
20110 Illnesses of mother             Categorical
20116 Smoking status                  Categorical

<table>
<thead>
<tr>
<th>Uplift Code</th>
<th>Uplifting Events Questions</th>
<th>Response Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>864</td>
<td>Number of days walked 10+ minutes</td>
<td>Ratio</td>
</tr>
<tr>
<td>874</td>
<td>How many minutes did you spend walking on a typical day</td>
<td>Ratio</td>
</tr>
<tr>
<td>884</td>
<td>Number of days doing 10+ minutes of moderate physical activities</td>
<td>Ratio</td>
</tr>
<tr>
<td>904</td>
<td>Number of days doing 10+ minutes more of vigorous physical activity</td>
<td>Ratio</td>
</tr>
<tr>
<td>971</td>
<td>How many times in the last 4 weeks did you go walking for pleasure?</td>
<td>Categorical</td>
</tr>
<tr>
<td>981</td>
<td>How long do you spend walking for pleasure</td>
<td>Categorical</td>
</tr>
<tr>
<td>991</td>
<td>Frequency of strenuous sport in the last month</td>
<td>Categorical</td>
</tr>
<tr>
<td>1011</td>
<td>Frequency of light DIY in the last 4 weeks</td>
<td>Categorical</td>
</tr>
<tr>
<td>1031</td>
<td>Frequency of friend/family visits</td>
<td>Categorical</td>
</tr>
<tr>
<td>1050</td>
<td>Time spent outdoors in summer (in hours, in a day)</td>
<td>Ratio</td>
</tr>
<tr>
<td>1060</td>
<td>Time spent outdoors in winter (in hours, in a day)</td>
<td>Ratio</td>
</tr>
<tr>
<td>2110</td>
<td>Ability to confide</td>
<td>Ordinal, 6-point Likert</td>
</tr>
<tr>
<td>2624</td>
<td>Frequency of heavy DIY in the last 4 weeks</td>
<td>Ordinal, 6-point Likert</td>
</tr>
<tr>
<td>6143</td>
<td>Transport type for commuting to job workplace</td>
<td>Categorical</td>
</tr>
<tr>
<td>6164</td>
<td>Types of physical activity in the last 4 weeks</td>
<td>Categorical</td>
</tr>
</tbody>
</table>

### 2.2.4. Curation of traumatic events

Questions from the online mental health questionnaire aimed to discern the impact of events per seven pre-defined categories as opposed to daily events. The UK Biobank online mental health questionnaire had 11 main sub-categories that were centered on mental distress, depression, mania, anxiety, addiction, alcohol use, cannabis use, psychotic experience, traumatic events, self-harm behaviors, happiness, and subjective
well-being. The predefined set of questions on traumatic events were used to discern traumatic events. There were 21 variables (as seen in Appendix 6.2, Table 12) of which 8 variables were excluded based on them being positively coded e.g., “Felt loved as a child” or if they pertained to symptoms of trauma exposure as opposed to trauma e.g., “Felt very upset when reminded of a stressful experience in the past month” – which resulted in 13 variables being retained as seen in Table 4, for details on binarization see Appendix 6.2, Table 13.

Table 4 Indicates the final list of traumatic events selected from the assessment center variables, with their respective codes.

<table>
<thead>
<tr>
<th>UK Biobank Online Mental Health Questionnaire</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Traumatic Code</strong></td>
</tr>
<tr>
<td>20488</td>
</tr>
<tr>
<td>20487</td>
</tr>
<tr>
<td>20490</td>
</tr>
<tr>
<td>20491</td>
</tr>
<tr>
<td>20523</td>
</tr>
<tr>
<td>20521</td>
</tr>
<tr>
<td>20524</td>
</tr>
<tr>
<td>20531</td>
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<td>20529</td>
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<tr>
<td>20526</td>
</tr>
<tr>
<td>20530</td>
</tr>
<tr>
<td>20528</td>
</tr>
<tr>
<td>20527</td>
</tr>
</tbody>
</table>

2.2.5. Discretization of life events & trauma

To understand the cumulative impact of the hassles and uplifts, each variable’s response was analyzed and discretized as 1 for the presence of a hassle or uplift, and 0 otherwise. The binarized cut-offs and their corresponding responses are detailed in Appendix 6.1, Table 11 for the 31 hassles and 15 uplifts. From this, the presence of a hassle or uplift were summed such that the maximum total hassle score was 31, and the maximum total
uplift score was 15. These cumulative hassles and uplift scores were used to assess the relationship between the life events and depression as inferred by their RDS-4 score. The 13 traumatic events were also discretized as 1 for the presence of a trauma and 0 otherwise. The binarized cut-offs and their corresponding responses are detailed in Appendix 6.2, Table 12.

2.2.6. Data dependencies and considerations

Several questions (variables) within the UK Biobank were only asked to some subjects (such as, if they answered yes to another question e.g., if answered yes gender of a female, they were then asked if they experience menopause), as such responses for males were coded as zero as opposed to missing data. After adjusting for such data discrepancies all subjects who did not have a depression score (RDS-4) were removed. However, despite these subjects having a depression score, ~55% of the sample had missing data for the 46 life events. As such the K-Nearest Neighborhood (K-NN) imputation method was used to fill in the missing data points with values that the participant was most likely to have put down based on all their responses. The K-NN Imputer from sklearn.impute was used, this was provided the mandatory parameter (n_neighbor) which tells the imputer the size of the parameter K. The fit_transform method was used on the imputer to impute the missing data. To ensure the correct value for K was selected, the imputer was optimized as follows by training many predictive models with different values of K. As the analyses aimed to use predictive modeling with regression algorithms for the target variable (depression measure: RDS-4), it is possible to train many predictive models where missing values are imputed with different values for K to see which one performs the best. The Scikit-Learn package was used to split the dataset into 70% for training and 30% for the testing subsets, to train the model, and validate it. The KNN algorithm was used to fit the model and then predictions were made on the test set. The Root Mean Square Error was computed from the testing dataset and upon evaluation, after averaging across the lowest values for the different K, the average optimum value was 29, which was utilized for the imputation.
2.2.7. Statistical models and multiple comparison correction

To assess the impact of the hassles and the uplifts on depression as measured by the RDS-4 score, a correlation was run on the summed scores for each individual, where both gender and sex were accounted for as covariates using scipy.stats and matplotlib.pyplot. A Spearman’s rank correlation was used given the presence of ordinal data which deemed Parsons’s correlation unsuitable. Using NumPy, heatmaps for both hassles & uplifts were created to enable further assessment of the spread of the correlation. Thereafter, a two-way analysis of variance (ANOVA) was run with main effects for the hassle score, uplift score, and interaction effect between the two, to discern whether there were any interactions between the hassles and uplifts using SciPy. These analyses were also run whilst controlling for the effect of traumatic events using an analysis of covariance (ANCOVA).

After discerning if there was a correlation between the RDS-4 and the summed hassles and uplifts scores, a ridge regression was run on the individual, unbinarized data (using sklearn.linear_model.Ridge) to find which hassles and uplifts had a greater relationship with the RDS-4 score. These analyses were run before and after controlling for the effect of traumatic events. The data was first demeaned through the preprocessing module of sklearn using StandardScaler. Once the dataset was split into a 70% training set and a 30% test set, Ridge() was used to fit the ridge regression model onto the training set. The performance of the model was evaluated by comparing the predicted and actual outcomes in the test sets and calculating the mean squared test error of the test set predictions. Given an array of lambda values ranging from very large to very small (which covered the full range of scenarios from the null model containing only the intercept to the least squares fit) was used, leave one out cross-validation was applied to tune the lambda via RidgeCV() – as opposed to arbitrarily choosing a value for lambda. Once the lambda with the smallest cross-validation error was found, the ridge regression model was refit on the dataset. For the ridge regression, a regularizer was applied given the degree of correlation between the variables. When tuning lambda for the combined model for hassles & uplifts, a λ of 0.047 was ascertained with mean squared error (MSE) = 0.080, compared to the independent models of hassles (λ= 0.035, MSE = 2.564) and uplifts (λ= 0.035, MSE = 2.564). The coefficient estimates were assessed and corrected
for multiple comparisons using the Bonferroni method through the statsmodels.stats.multitest module. This was done for all life events, with and without the inclusion of trauma in the model. All hassles and uplifts that remained significant after correction were plotted on a bar chart using matplotlib to assess their distribution.

2.3. Results

Below are the results assessing the relationship between hassles and uplifts and their relationship with depression before (n = 19,829) and after (n = 13,625) controlling for traumatic events. Correlations provide a sense of the relationship between life events and depression, whilst ANOVA analyses highlight the interaction effects. The regression analyses indicate the independent effects each life event has on depression before and after controlling for traumatic events.

2.3.1. How are life events related to depression

A Spearman's rank-order correlation indicated a positive correlation between the sum of hassles and the RDS-4, which was statistically significant \( rs(19,827) = 0.24, p = 5.07E-298 \) as seen in Figure 6A. Furthermore, a negative correlation was seen between the sum of uplifts and the RDS-4, which was also statistically significant \( rs(19,827) = -0.14, p = 4.84E-86 \) as seen in Figure 6B. Both correlations remained significant after controlling for traumatic events \( rs(19,827) = 0.22, p = 1.20E-250 \) for hassles and \( rs(19,827) = -0.12, p = 1.83E-50 \) for uplifts.
Figure 6. Depicts scatterplots of the relative distributions between A. cumulative hassles and the RDS-4 and B. cumulative uplifts and the RDS-4.

2.3.2. Interaction effects between hassles and uplifts

A two-way analysis of variance yielded a significant main effect for hassle scores $F(25,19569)= 20.461, P = 6.04E-183$. There was also a significant main effect of the uplift score $F(15,19569)= -9.218, P = 6.25E-102$. There was a significant interaction effect between hassles and uplifts $F(219,19569)= 1.885, P = 6.32E-621$. These results remained significant after controlling for traumatic events ($f(219,19568)= 1.581, p = 4.38E-421$).

2.3.3. Which life events contribute to an individual’s depression level

The ridge regression model for hassles, uplifts, and both combined using the $\lambda$ chosen by cross-validation was run and Bonferroni correction was applied to examine the significant coefficient estimates as seen in Table 5 below. The hassles group had a greater total $R^2$ value accounting for a greater percentage of variation explained by the regression model when compared to uplifts, however, the combined hassles + uplifts model was marginally better (0.31). This result also holds when the adjusted $R^2$ was used to account for the number of predictors in the model. The F-statistics for all groups were significant indicating that all the models provide a better fit than the intercept model alone. More so, when including trauma in the models a small increase in variance explained was noted for hassles (0.23), and a small decrease in variance was noted for uplift (0.09) and the combined model (0.30).
Table 5 Indicates R2, adjusted R2 values along with the F-Statistic for the number of features for each group to 2 d.p. The asterisk (*) indicates a significant value (<0.05).

<table>
<thead>
<tr>
<th>Analyses</th>
<th>Adjusted R2 Value</th>
<th>Adjusted R2 Value with Trauma</th>
<th>F-Statistic</th>
<th>Number of Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hassle</td>
<td>0.21</td>
<td>0.23</td>
<td>146.23*</td>
<td>31</td>
</tr>
<tr>
<td>Uplift</td>
<td>0.13</td>
<td>0.09</td>
<td>84.95*</td>
<td>15</td>
</tr>
<tr>
<td>Hassles &amp; Uplifts</td>
<td>0.31</td>
<td>0.30</td>
<td>107.65*</td>
<td>46</td>
</tr>
</tbody>
</table>

A similar group of hassles and uplifts were significant when running the ridge regression using the individual and combined groups. When running the ridge regression using combined hassles a similar group of hassles and uplifts were significant when controlling for traumatic events as seen in Table 6. For results of individual group analyses see (Appendix 6.3, Table 13).

Table 6 Indicates Bonferroni corrected (<0.05) P value, T value, and R2 value for hassles and uplifts from the combined group's analyses with and without trauma (to 2 d.p or 1 s.f.). The shaded rows indicate significant life events (<0.05).

<table>
<thead>
<tr>
<th>Regression Analyses</th>
<th>Combined Hassle &amp; Uplift</th>
<th>Combined Hassle &amp; Uplift controlled for traumatic events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hassles</td>
<td>P Value</td>
<td>T Value</td>
</tr>
<tr>
<td>Accommodation Lived in</td>
<td>0.06</td>
<td>4.69</td>
</tr>
<tr>
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<td>Uplifts</td>
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<td>Mins Spent Walking in A Day</td>
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<tr>
<td>Chest Pain or Discomfort</td>
<td>No Of Days of Vigorous Physical Activity Ten Plus Mins</td>
<td></td>
</tr>
<tr>
<td>Attendance Disability Mobility Allowance</td>
<td>Time Spent Walking for Pleasure</td>
<td></td>
</tr>
<tr>
<td>Mouth/Dental Problems</td>
<td>Frequency Of Visits Friends Family</td>
<td></td>
</tr>
<tr>
<td>Pain Type Experienced in Last Month</td>
<td>Time Spent Outdoors in Winter</td>
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<tr>
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<td>Ability To Confide</td>
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<tr>
<td>Frequency Of Heavy DIY in the Last Month</td>
<td>Type Of Physical Activity in Last Month</td>
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<th>P Value</th>
<th>T Value</th>
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<td>0.007</td>
<td>0.07</td>
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<td>No Of Days of Vigorous Physical Activity Ten Plus Mins</td>
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<td>Time Spent Walking for Pleasure</td>
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<tr>
<td>Time Spent Outdoors in Winter</td>
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<td>4.34</td>
<td>6.31E-05</td>
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<td>0.006</td>
<td>0.06</td>
<td>0.63</td>
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The combined analyses indicated that hassles related to health and perceptions of health such as overall self-health rating, hearing difficulty with background noise, and pain type experienced in the last month had the greatest contributions as seen in Figure 7.

Figure 7. Depicts bar graphs thresholded at a high depression level (RDS-4 = 8) as discerned by the RDS scale (range: 4-16). The x-axis indicates answer categories per question, and the y-axis indicates the proportion of participants for each possible answer. (A) Negative Perceptions of Overall Self-Health are related to a Higher RDS. (B) The presence of hearing difficulties relates to a higher RDS-4. (c) Pain experienced in the last month.

The combined analyses indicated that uplifts related to the ability to confide and the frequency of family and friend visits had the greatest contributions as seen in Figure 8.

Figure 8. Depicts bar graphs thresholded at a high depression level (RDS-4 = 8) as discerned by the RDS scale (range: 4-16). The x-axis indicates answer categories per question, and the y-axis indicates the proportion of participants for each possible answer. (A) Having Someone to Confide in Frequently Throughout the Week is Linked to a Lower RDS (B) Frequency of Family & Friend support.

2.4. Discussion and Significance

Results suggested social support and ability to confide were the most significant uplifts in relation to low RDS-4 scores, and hassles related to health and health conditions were
the most significant when individuals had a high RDS-4 score. Thus, by preventing health conditions and nurturing social support networks to enable the ability to confide all serve as possible economic targets to combat depression. More so, the inclusion of trauma did not change the association between life events and depression.

2.4.1. Health related hassles and social support uplifts impact depression

The results indicate a positive correlation between the number of cumulative hassles and depression severity as discerned by the RDS-4 score and a negative correlation between the number of cumulative uplifts and the RDS-4 score. There was also a significant interaction effect between the hassles and uplifts, and their impact on the RDS-4 score indicating that one variable is dependent on the level of the other variable, consequently, this highlights the need to consider both hassles and uplifts when considering their impact on depression. The effect sizes for the individual hassles and uplifts are relatively low, but significant, which is expected given the variance in mental health data. The cumulative hassles and uplifts were able to account for a larger amount of the variability in the RDS-4, (31%), with cumulative hassles accounting for a larger proportion of the variability (21%) when compared to the cumulative uplifts (13%), as seen in Table 5. These results are in line with previous studies reporting that individuals who experience more uplifts have fewer depressive symptoms than those experiencing fewer uplifts (Ravindran et al., 2002; Vargas & Arnett, 2010), and individuals who experience more hassles have greater depressive symptoms than those experiencing fewer hassles (Ravindran et al., 2002).

Our results show that cumulative hassles and uplifts account for 31% of the variance in depression score, but individual events had minimal contribution independently (as reflected by their R2 value seen in Table 6). This is in line with the idea that all these hassles and uplifts accumulate and have an impact on the RDS-4 scores for individuals. Additionally, the combined hassles and uplift model did not explain that much more variance than the hassle model alone (which indicates that hassles have a greater effect on RDS-4 when compared to uplifts. It could also be the case that the hassles encapsulated in the curated set have a greater subjective impact when compared to the
uplifts, which would be in line with the notion of negativity bias (Baumeister, Finkenauer, Vohs, 2001). Furthermore, there were 16 fewer uplifts compared to hassles, which could also account for the low contribution, and to mitigate the impact of hassles, a greater number of uplifts may be required.

The greatest hassle was the overall perception of one's health where results indicated that poorer physical health was linked to higher depression scores in this cohort. Given the UK Biobank represents an older cohort, it is to be noted that as many individuals start to age, they do begin needing more assistance with everyday tasks. Previous studies have shown how self-efficacy can act as a mediator of the effects of daily stressors on mental health, with superior effect sizes for positive compared to negative mental health (Schonfeld et al., 2016). As such, therapy or mindfulness meditation could be an economical option to support and manage an individual's overall perceptions of their health. Furthermore, those who had a hearing difficulty had a higher RDS-4 score when compared to those who did not. Statistics indicate that hearing impairment is the third most prevalent chronic health condition in people over 65 years of age (WHO, 2020). Hearing impairments in older adults are reported to make them more vulnerable to mental health problems including depression and can result in social isolation (Mumtaz & Saqulain, 2019), which could impact their ability to communicate with others. When looking at the pain type in the last month, head, shoulder, abdominal, facial, and full body resulted in a greater RDS-4 score, when compared to back, and joint pains in the knee and hip pains, which is in line with previous studies that have reported that chronic joint pain and back pain are common physical symptoms in depression (Trivedi, 2004), such that these other pain types could contribute to lower mood.

In relation to uplifts, the single largest contributor was the ability to confide, which indicated that as the ability to confide increased the RDS-4 score decreased. This is expected as social support is reported as a protective measure against depression, with Ioannou, Kassianos & Symeou, (2019) reporting perceived social support from friends being related to significantly lower depression symptoms. This explained the second largest contributing uplift which was the frequency of friends and family visits. A markedly lower RDS-4 score was seen in those who had a family or friend visit 2 to 4 times a week than those who had someone visit once a week or less. Loneliness is a
common experience in the elderly, as 40% of those above 65 years of age report loneliness at least sometimes in their life, where older lonely individuals left untended resulted in serious consequences for their mental health (Mushtaq et al., 2014). Furthermore, individuals who had contact with friends and family once a week or more had a lower RDS-4 score when compared to those who had contact once a month, or less. Previous research has shown how family and friends can help reduce the level of depression experienced through being a confidant (Grifth et al., 2011). As such, providing a support network either through sports/leisure activity or the ability to confide would be an inexpensive way to reduce mental health conditions in the elderly population. Additionally, time spent walking for pleasure was associated with a lower RDS-4 which is in line with previous research which indicates that walking more often during the day helps to keep depression rates lower (Otto & Smits, 2011).

Taken together, social interactions were the most significant uplifts in relation to low RDS-4 scores, and hassles related to self-perceptions of health and health conditions were the most significant when individuals had a high RDS-4 score. Thus, by preventing health conditions, engaging in social activities, and having a support system that enables the ability to confide could all be economic targets to combat depression.

### 2.4.2. The impact of life events depression is independent of trauma

In relation to the overall group-level regressions, when run separately, the total variance in depression explained by hassles and uplifts were, 21% and 13%, respectively (see Table 5). When including both life events in the same model, these life events accounted for 31% of the total variance in depression, which was marginally better. The addition of trauma did not substantially change the results in either analysis. Nonetheless, small changes were noted in the adjusted R-square value when trauma was added suggesting that trauma may have some limited influence on the overall variance in RDS-4 scores. A slight increase in the total variance explained by hassles was observed when controlling for trauma (from 0.21 to 0.23), suggesting trauma may still have some small contributions to the model, however, the increase is too small to say for certain. More so, the adjusted R2 value decreased from 0.13 to 0.09 for uplifts when trauma was included in the model, which suggests that trauma may have a more significant role in predicting
depression in the context of uplifts. In other words, the effect of trauma on uplifts may outweigh the potential protective influence they have on mental health. This suggests that trauma may be a relevant predictor variable for depression in the context of uplifts. In general, the results suggest that hassles have a stronger association with depression than uplifts, as indicated by the higher R2 value in the hassle analysis. Taken together, the addition of trauma did not substantially change the results in either analysis.

The results of the regression analyses of individual life events indicate that when controlling for traumatic events, the same 3 hassles remained significant which included: overall general health rating, hearing difficulty problems with background noise, and pain type experienced in the last month. Furthermore, when controlling for traumatic events, the same 2 uplifts remained significant: frequency of visits from friends & family and the ability to confide. However, one additional uplift became significant: time spent walking for pleasure became a significant predictor. It is possible that trauma may affect one’s ability to engage in pleasurable activities like walking for pleasure, leading to a reduced impact of this uplift on depression. A study by Peat, McCarney & Croft in 2001 reported a prevalence rate of 10% for painful disabling knee osteoarthritis in those aged over 55. More so, in this sample, as seen in Figure 7C, a greater proportion reported a higher RDS-4 score associated with knee pain. This knee pain experienced may influence how individuals perceive and engage in the uplift of walking for pleasure which in turn impacts their depression (if they are unable to go outside or walk around and meet people). These results suggest that the impact of cumulative hassles and uplifts on depression are not dependent on trauma and exist independent of traumatic events experienced.

2.5. Significance, Limitations, and Future Direction

In summary, this study revealed that cumulative hassles explain a large proportion of variance in depression scores. Furthermore, the findings showed that the relationship between depression and hassles is largely independent of trauma. Overall, these results suggest that it is important to consider the impact of both hassles and uplifts on depression as they persist even after controlling for traumatic events. This can have implications for the prognosis of depression and effective care for patients.
2.5.1. Significance

Social support and frequency of friends and family visits were the most significant uplifts in relation to low RDS-4 scores, and hassles related to health and health conditions were the most significant when individuals had a high RDS-4 score. However, as there is minimal research into the cumulative impact of a group of life events on depression, it was not unknown what the relationship would be. This is the first study to explicitly investigate the relationship between a group of cumulative hassles and uplifts with depression. More so, these results hold independent of the amount of trauma experienced by an individual. Thus, by preventing health conditions and nurturing social support networks to enable the ability to confide all serve as possible economic targets to combat the onset and progression of depression.

2.5.2. Limitations

Despite the advantages of the UK Biobank, such as using a large-scale diverse phenotypic sample, the availability of multiple domains of hassles/uplifts enabling the cumulative scoring, and the availability of variables to develop an RDS-4 score, multiple limitations are worth noting. The first includes the fact that 55% of subjects had missing data for life events. Although the K-NN method was used to fill in the missing data points it is worth noting that the value of “k” is usually a limitation when a large proportion of data is missing. If the value of “k” is too high to the relative data it may lead to imputations that are less accurate or biased as the points may not be truly representative, and if the value of “k” is too small, the results of the imputation may be over-influenced by a few nearby points leading to potential overfitting or local patterns captured in the data that not generalizable. The second limitation is that the analyses were performed at one timepoint, and it is unknown how generalizable these results are. The third limitation is that the complexity of the relationship between the breadth of life events and depression means that other confounds should also be accounted for (e.g., genetics). The fourth limitation is that the number of uplifts was lower than the number of hassles, which may contribute to the lower explained variance in the depression score of cumulative uplifts. The last limitation is that hassles/uplifts were somewhat correlated, which may reduce
the ability of the linear model to distinguish the effects of some individual hassles/uplifts. Nevertheless, to retain the interpretability of individual life events the project avoided orthogonalization or data reduction techniques.

2.5.3. Future Direction

Future work may wish to expand the number of uplifts considered, to balance the number of life events being investigated. To discern the interpretability of a group of life events, studies could choose to employ data reduction techniques such as principal components analysis. More so, given the lack of research in the field, research should be conducted at other timepoints based, as more data has been made available longitudinally by the UK Biobank. Lastly, future studies should utilize the full breadth of variables in the UK Biobank to control for confounds and assess the complex relationship that contributes to the relationship between life events and depression.
Chapter 3: Network based PROFUMO correlates of depression

Brain network studies consistently report disruptions of resting-state networks (RSNs) in patients with depression. However, studies rarely dissociate between state & trait-based depression to discern their neural correlates. This chapter motivates the need to distinguish between state and trait depression when investigating resting state network-based changes in depression using fMRI. This is followed by details of an underutilized methodology: probabilistic functional mode (PROFUMO), to discern RSNs which are used in a study to investigate the neural correlates of depression – after controlling for the effect of traumatic events. Details of the methodology used and the subsequent results and their significance are discussed.

3.1. Background and Motivation

3.1.1. Network based studies of depression

Resting state brain networks encompass a set of brain regions that show synchronized activity during the lack of a specific stimulus when the person is not engaged in a particular task, i.e., at rest. These networks, such as the Default Mode Network (DMN), Salience Network (SN) & Fronto-parietal network (FPN), can be identified using fMRI. Network-based changes refer to changes in connectivity/functional interactions between different regions in the brains that are either between or within a resting-state network. Lord et al. (2012) found changes in the group structure of resting-state functional connectivity in unipolar depression patients which suggested that changes in the organization of functional networks may be related to depression. Hamilton et al.
(2011) used multivariate Granger causality analysis to investigate neural primacy in depression and found evidence of causal influence between the prefrontal cortex and other brain regions, suggesting that changes in directed functional connectivity may be related to depression. Cao et al. (2019) found altered functional connectivity within the default mode network in geriatric depression patients with cognitive impairment compared to healthy controls, which suggested that cognitive deficits in depression may be related to changes in network connectivity. Some studies have also focused on gender-based changes in relation to depression, where Dawson et al. (2018) found that emotion-related impulsivity and rumination predicted the severity and trajectory of symptoms in women with a history of major depression during the perimenstrual phase; highlighting the potential importance of emotional regulation in networks implicated depression. Whilst others have focused on the impact of treatment as seen in Li et al. (2021) where their study found aberrant functional connectivity within the default mode network in drug-naive patients with major depressive disorder before and after eight-week antidepressant treatment, suggesting that changes in network connectivity may be related to the therapeutic effects of antidepressants. Taken together, research over the years has shown functional connectivity has had a casual impact on depression.

In addition to depression-related changes in functional connectivity, there is also a large body of literature which consistently reports these findings. Research into functional connectivity changes in depression have indicated the importance of the DMN and SN. This was seen in the study by Sheline and colleagues in 2009 which aimed to investigate alterations in brain network connectivity in adults with major depressive disorder (MDD). The study included 21 adults with MDD and 21 healthy control participants. The results of the study showed reduced connectivity in the DMN and increased connectivity in the SN, in adults with MDD, compared to healthy controls. Researchers found decreased connectivity between the medial prefrontal cortex and posterior cingulate cortex within the DMN, and increased connectivity between the dorsal anterior cingulate cortex and insula within the SN. These findings suggest that altered network dynamics may play a role in the pathophysiology of depression, and may contribute to cognitive and emotional dysregulation in the disorder. In 2011, Andreescu and colleagues investigated changes in brain network connectivity within older adults with remitted depression. They had 25 older adults with a history of major depressive disorder (MDD)
who were in remission, and 25 age- and gender-matched healthy controls. The results of the study showed reduced connectivity in the DMN in older adults with remitted depression, compared to healthy controls. Specifically, the researchers found decreased connectivity between the medial prefrontal cortex and posterior cingulate cortex within the DMN.

Alongside changes within the DMN & the SN, several studies have also reported changes between these two networks when investigating depression. This was seen in a study by Wang and colleagues in 2019 which aimed to investigate the relationship between the SN and the DMN in MDD. The study included 63 patients with MDD and 60 healthy controls. These results indicated increased functional connectivity between the dorsal anterior cingulate cortex (a key node of the SN) and the precuneus (a key node of the DMN) in patients with MDD, compared to healthy controls. This increased connectivity was also associated with higher levels of depressive symptoms and rumination in the MDD group suggesting altered SN-DMN connectivity may contribute to the cognitive and affective symptoms of depression. More so, a meta-analysis of recent fMRI studies into depression proposed a model that incorporates changes in functional connectivity within current hypotheses of network dysfunction in extreme depression (Kaiser et al., 2015). Another meta-analysis of 36 studies reviewing resting state functional connecting in MDD reported 3 consistent findings in relation to changes in network connectivity relating to the DMN & SN, this includes: an increase in connectivity within the anterior DMN; a decreased connectivity between the SN & DMN; a change in between the connectivity anterior and posterior DMN (Mulder et al., 2015). These findings correspond to the current understanding of depression as a network-based disorder in relation to these 2 specific networks. Taken together, it is crucial to examine alterations in both the SN and the DMN when studying the neural correlates of depression.

3.1.2. Dissociating state and trait depression

When reviewing studies into network-based changes in depression, it is unclear whether these studies are sensitive to trait depression or state depression and therefore the differential neural correlates of state and trait level depression are unknown. As mentioned in Chapter 1, Section 3.2. state depression refers to the current symptoms an individual experiences which are temporary in nature, with extended periods of changes
in depression levels that are more responsive to changes in the individual's environment or circumstance (Chiappelli et al., 2014). Whereas trait depression can be thought of as a general propensity throughout one's life, and as such is more stable in nature, and contribute to long-term individual difference in the risk of developing depression (Chiappelli et al., 2014). The lack of research into the dissociation between state and trait depression in the literature is largely due to the high correlation reported between the two types of depression in cross-sectional studies being greater than 0.5 (Ormel et al., 2004; Bagby et al., 2008; Kotov et al., 2010; Dutt et al., 2021). This high correlation highlights that the relationship between neuroticism and depression is complex and needs further research to be fully understood. More so, the high correlation is compounded by the fact that state and trait depression are not completely independent constructs, and that one can influence the other. Nevertheless, it is important to study potential dissociable neural correlates of state and trait depression because it will better help us understand the underlying mechanisms of depression and potentially improve personalized treatment options for depression.

Trait level depression can be measured using the personality trait of neuroticism, which is characterized by a tendency to experience negative emotions such as anxiety and sadness (Klein, Kotov & Bufferd., 2011). In 2003, Caspi and colleagues conducted a study that investigated the relationship between stress and brain function in young adults with high and low levels of neuroticism. Participants completed measures of neuroticism and stress and underwent fMRI scanning whilst performing an emotional face-matching task. The results showed that participants high in neuroticism had increased amygdala activation and decreased prefrontal cortex activation in response to emotional faces, compared to those low in neuroticism. These findings suggest that the neural mechanisms underlying stress and emotion processing may be altered in individuals with high levels of neuroticism, which may contribute to a greater susceptibility to depression and anxiety. Another study by Rive and colleagues in 2013 investigated the relationship between neuroticism and brain structure in patients with MDD. The study included 71 patients with MDD, who underwent MRI to measure brain structure and completed measures of neuroticism and depression severity. The results showed that neuroticism scores were significantly correlated with decreased gray matter volume in regions of the prefrontal cortex and anterior cingulate cortex, which are regions involved
in emotion regulation and executive function. These findings suggest that neuroticism may be a useful index of trait-level depression severity, and may help to identify individuals at risk for developing MDD. Another study also reported individuals high in neuroticism had increased amygdala activation and decreased prefrontal cortex activation in response to negative emotional faces, compared to those low in neuroticism (Habel et al., 2010). This suggests that individuals with high trait neuroticism may have a heightened sensitivity to negative emotional stimuli and may have difficulty regulating their emotional responses. These findings do overlap with the findings of studies investigating the neural correlates of depression. Specifically, individuals with high trait neuroticism in this study showed increased amygdala activation in response to negative emotional faces – a finding that has been consistently reported in studies investigating depression (e.g., Sheline et al., 2001; Rive et al., 2013). Additionally, the decreased prefrontal cortex activation in individuals with high trait neuroticism in these studies are also consistent with findings from studies of depression that have reported decreased prefrontal cortex activation during emotional processing tasks (e.g., Keedwell et al., 2005). Therefore, while not identical, these results do highlight the overlap in the brain regions and processes involved in both trait neuroticism and depression.

Neuroticism and depression are often closely related constructs, with some studies that indicate them sharing a common genetic and neural basis (Adams et al., 2020; Joseph et al., 2021) whilst others use them interchangeably in research. However, neuroticism is a known predictor of pathological psychology such as depressive symptoms (Xia et al., 2011; Liu, Chen & Chen, 2020). Individuals who score high on neuroticism are at an increased risk for developing depression due to their higher likelihood of experiencing stressful events (Liu, Chen & Chen, 2020). High neuroticism is also associated with a higher risk for onset, increased symptoms severity, and a more chronic course of depression. (Navrady et al., 2017; Liu, Chen & Chen, 2020; Lahey, 2009). Despite their close relation, it should be noted that neuroticism is a risk factor for depression, whereas depression is a mood disorder characterized by a specific set of symptoms that can change over time (Jylhä and Erkki, 2006; Vinberg & Kessing, 2006). State depression is characterized by increased activity in the amygdala, a brain region involved in the processing of emotions, and decreased activity in the DMN (Zhang et al, 2018; Li et al, 2018). Trait depression is characterized by increased activity in the amygdala and the
In order to differentiate between the neural correlates of trait and state depression, longitudinal imaging data can be utilized. This is because state depression is expected to change over time, whilst trait depression (which is indexed by the neuroticism personality trait) is stable over time. The UK Biobank dataset holds neuroimaging data at several timepoints over several years, which allows for a longitudinal study that would help achieve the dissociation between state and trait depression by focusing on those individuals who have the bigger changes in state depression over time. This is a sample that is typically hard to come by, however, the size of the UK Biobank allows for the ability to discern these subjects. By using those with a large change in depression over time, the correlation within the UK Biobank dataset between the state and trait measures (RDS-4 and Neuroticism, respectively) drops from 0.67 to 0.16. Furthermore, the approach of using those with the largest changes as opposed to all participants with changes in depression (i.e., small changes too) is that the latter may not be an accurate representation of state depression, and may be subject to measurement error, whilst the larger changes are more likely to be accurate and more easily detected and as such, would help to improve the reliability of the results. Such a longitudinal dissociation requires a continuous depression measure as opposed to a discrete measure to account for such changes. This is possible with the use of the RDS-4 score within the UK Biobank dataset, which has a scale that ranges from 4 to 16, with 4 indicating no depression and 16 indicating severe depression. Access to the RDS-4 score as a state measure of depression and access to neuroticism data as a trait measure within the UK Biobank allows for the research into dissociating state and trait depression. In this way, the use of large changes in state depression (>± 2) helps to ensure that the results reflect the true differences in state and trait depression and provides a clearer understanding of the relationship between the two; as state and trait depression are often highly correlated and challenging to dissociate.
3.1.4. PROFUMO outputs

In order to discern the neural correlates of state & trait depression, PROFUMO will be utilized to define brain networks. PROFUMO estimates AMPs, Netmats, and Spatial Overlap Matrix in the same data decomposition, using the outer product model for more details refer to Chapter 1 Section 3.5.

The main PROFUMO outputs (as seen in Figure 9) considered during this project includes amplitudes (AMPs) which indicate the signal strength of a mode (i.e., how strong that network is for each individual). Next, Netmats which is the connectivity matrix that takes the timeseries from 2 modes and computes a correlation between them. The final output is a spatial overlap matrix that explains the degree of spatial organization between the different spatial maps (describing the spatial layout within a mode) using the correlations computed. Thus, to assess the neural correlates of depression these PROFUMO outputs can be used as targets in the regression model.

![Figure 9. Visualizations of PROFUMO output including amplitudes (AMPs), network matrices (Netmats), spatial maps, and spatial overlap matrix (from left to right).](image)

Given that network matrices are timeseries-based, they change quickly and thus are hypothesized to relate to state depression, which changes with time, whereas spatial maps are related to network structure which are not expected to change as rapidly therefore, they are hypothesized to relate to trait depression. More so, it is unknown how rapidly amplitudes may change, but they are reported to have a strong test-retest reliability (Dutt et al., 2021) and therefore could be hypothesized to be more closely related to trait depression. Recent findings have indicated that spatial information derived from PROFUMO was most strongly linked to individual differences in behavior in healthy subjects and variability in spatial overlap matrices between complex cortical
networks was a key source of behaviorally-relevant information (Bijsterbosch et al., 2019). Thus, PROFUMO may be better suited to discern the differential neural correlates of state and trait depression. Therefore, it is of interest to test the potential value of this method for identifying markers of mental health symptomatology as PROFUMO was developed relatively recently and has not yet been tested in mental health population. Therefore, in this study it is postulated that spatial overlap in the DMN and the SN would most likely be linked to trait depression and network matrix connectivity between the DMN and the SN will be linked to state depression.

3.1.4. Underlying assumptions of PROFUMO and implementation considerations: Spatial Maps & Dimensionality

Dissociating state and trait depression can be done via the use of longitudinal data within the UK Biobank (as discussed in Chapter 3, Section 1.2.) using those who have a large change in depression over time (as measured by the RDS-4). More so, to discern the neural correlates of state and trait depression, PROFUMO can be used to discern resting state networks. However, it is important to note when using PROFUMO that it has not yet been tested longitudinally and as a result has some underlying assumptions and implementation which need to be considered for such a study design. In the literature (Bijsterbosch et al., 2019; Harrison et al., 2015) PROFUMO has previously been implemented with the assumption that the spatial organization of the brain does not change longitudinally. As PROFUMO has not been used in a longitudinal study, one would loosen this assumption and allow for the spatial organization to vary if the data supports this; particularly with the aim to discern the PROFUMO neural correlates of longitudinal depression over time. One would expect the brain to have some changes registered over time simply due to growth and aging, not including other life events. Due to this implementation choice, PROFUMO generates 1 spatial map per person incorporating information across all timepoints. As such, for the studies mentioned in Chapter 3 and 4, PROFUMO was run such that the data was treated as a separate subject. These maps can then be inspected to discern if there are any longitudinal changes, which would in turn indicate the need for the generation of separate spatial maps at each timepoint.

Another factor, not limited to PROFUMO, is the lack of consensus on the dimensionality that should be used in the field of neuroimaging. Dimensionality refers to the number of
networks used to decompose the fMRI data such that higher dimensions indicate lower stability because they relate to smaller modes in PROFUMO, which cover fewer brain voxels. Dimensionality can affect the results of the analysis, and there is no consensus on the optimal dimensionality in neuroimaging. Some researchers suggest that the dimensionality should be chosen based on the number of brain regions of interest (Diedrichsen, Wiestler & Ejaz, 2013) whilst others suggest that it should be chosen based on the degree of spatial independence of the independent components (Wang, Peng & Li, 2015). The estimation of the dimensionality is a challenging task and despite the proposed methods to estimate it (such as the minimum description length criterion, the approximate criterion, the kurtosis criterion, and the stability criterion) they are not always reliable and may lead to different estimates of dimensionality. Given that optimal dimensionality remains a topic of ongoing research and debate in the field of neuroimaging, it is important to also test which dimensionality provides the most stable network maps. One would hypothesize that lower dimensionality will relate to higher stability, as there are larger modes and thus more brain voxels being covered. Therefore, it is important to test which dimensionality provides the most stable network maps (see Chapter 3, Section 2.2, for results).

3.2. Methods

Underlying assumptions of spatial stability longitudinally was assessed through visual inspection, whilst PROFUMO's dimensionality was optimized based on the split-half reliability method (reported in Chapter 3, Section 2.2). Thereafter, regression analyses were used to discern the neural correlates of state depression and trait depression whilst controlling for confounds. Lastly, significant PROFUMO outputs were inspected to discern what brain networks were involved.

3.2.1. Dataset

Longitudinally, RDS-4 scores were available for 2594 individuals, of which 2391 also had imaging data at both timepoints. Of the 2391 individuals, 98 had a decrease in RDS scores from timepoint 1 to 2, which varied from a magnitude of between 3 to 8 points, whilst 95 had an increase in RDS score from timepoint 1 to 2, which varied from a magnitude
of between 3 to 12 points. Those with a change between -2 and 2 inclusive, were excluded (n = 2195). Thus, 193 individuals were retained for Aim 2.

**Longitudinal changes in depression**

In considering longitudinal studies into changes in state-based depression, one could simply subtract the depression score derived at one timepoint from another. However, this method does not account for baseline RDS. It is possible to obtain a residual score that removes the effects from the original score. This is considered to be a better method as it allows for a more precise assessment of the relationship between the variables of interest as it addresses common problems associated with difference scores such as regression to the mean, measurement errors, and ceiling/floor effects (Castro-Schilo and Grimm, 2017). To calculate a residualized change score for depressive symptoms, the method described by Castro-Schilo and Grimm (2017) was followed. A simple linear regression model was run with depressive symptoms at timepoint 2 as the dependent variable and depressive symptoms at timepoint 1 as the independent variable. The residuals from this model were saved, which represents the unexplained variability in depressive symptoms at Time 2 that is not accounted for by depressive symptoms at Time 1. Next, the residuals were used as the measure of change in depressive symptoms. This method allowed the isolation of the change in depressive symptoms that was not accounted for by its initial level and examines the effects of other predictors on change over time.

**3.2.2. PROFUMO dimensionality determination: Split-half reliability method**

To discern which PROFUMO dimensionality is most stable, a split-half reliability method was used to measure internal consistency. The subjects (n=193) were randomly split into two halves (n=97, n =98) and PROFUMO was run separately in each split at 5 different dimensions from 10 to 50 increasing in increments of 10. The resulting PROFUMO group maps and the whole-brain mask were reshaped to a 2D vector via the Nibabel package. Then a correlation was taken between the two split halves and inputted into the Munkes package which applies the Hungarian Algorithm to solve the assignment
problem – which orders the PROFUMO group maps into the best match across the split-half repeats. Then the mean split-half spatial correlation and the number of PROFUMO group maps with a split-half correlation above $r=0.50$ and $r=0.95$ were investigated.

To run PROFUMO, the preprocessed (Alfaro-Almagro et al., 2018) resting state scans were registered to Montreal Neurological Institute (MNI) Space. Next, homogeneous smoothing was performed on the registered images using several masks including cortical, subcortical, and cerebellum masks. This step is done to increase the signal-to-noise ratio in the image and then implemented through a Gaussian kernel with a specification of full width at half maximum (FWHM = 6). Thereafter, PROFUMO was run to estimate separate spatial maps for each subject at each timepoints as differences were noted at each timepoint.

### 3.2.3. Statistical models for dissociating state and trait depression

#### 3.2.3.1. Regression model to discern state depression

To discern the differential PROFUMO correlates of state depression, regressors that were related to state depression (i.e., RDS residuals) & trait depression (i.e., neuroticism mean over timepoint 1 and timepoint 2) were identified along with any confound regressors that could be used to predict the PROFUMO output. Given the correlation between neuroticism and change in depression over the two timepoints is lower ($0.16$), both these variables could now be included in the same regression model. More so, four confound regressors were also included: 1) mean age across both scans, as this could impact their depression with older individuals likely to have a better coping mechanism and to control for age differences; 2) gender, to control for sex differences; 3) days between scans, given this was a longitudinal analysis; 4) mean head motion across both scans (scan 1 – scan 2 correlation was $0.76$, suggesting relative stability). Thus, the regression model used is as seen in 3.1. Prior to inclusion in the regression analysis, all regressors were z-scored (for the PROFUMO spatial overlap correlation, a Fisher’s $r$-to-$z$ transformation was conducted) to standardize their scales and make them comparable in terms of their unit measurement.

\[
Y = \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_3X_3 + \beta_4X_3 + \beta_5X_5 + \beta_6X_5. \tag{3.1}
\]
Where \( Y \) = PROFUMO measures of interest (Amplitude, NetMats, and Spatial Correlation Matrix), \( \beta_0 \) = the intercept, \( X_1 \) = RDS residuals, \( X_2 \) = Mean Neuroticism, \( X_3 \) = Mean Age \( X_4 \) = Sex, \( X_5 \) = Number of Days between Scan \( X_6 \) = Mean Head motion.

3.2.3.2. Regression model to discern trait depression

To discern the differential PROFUMO correlates of trait depression, a regression analysis was run using data from timepoint 1. The RDS-4 was excluded from the analysis due to its high correlation with Neuroticism (r= 0.76). As such the regression analyses were run at both timepoints without the inclusion of RDS to ensure neural correlates of trait were being investigated. More so, the number of days between scans was also removed as this became a cross-sectional study not focused on change overtime. Thus, the regression models used are as seen in equations 3.2 and 3.3 for timepoint 1 and 2, respectively. Prior to inclusion in the regression analysis, all regressors were z-scored (for the PROFUMO spatial overlap correlation, a Fisher's r-to-z transformation was conducted) to standardize their scales and make them comparable in terms of their unit measurement.

\[
Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4.
\]  
(3.2)

Where \( Y \) = PROFUMO measures of interest (Amplitude, NetMats, and Spatial Correlation Matrix), \( \beta_0 \) = the intercept, \( X_1 \) = Neuroticism, \( X_2 \) = Age at relevant timepoint \( X_3 \) = Sex, \( X_4 \) = Head motion at relevant timepoint.

3.2.4. Relocating brain networks of interest

To discern the brain networks that were active for significant regression within the 136 netmat edges and 136 spatial overlap correlations unravel.index() was used to relocate their location in the 17 x 17 matrix. Thereafter, the 3 noisy modes were included to relocate the modes of interest. Fsleys was used to visualize significant edges and spatial overlap correlations. To discern the brain networks that were active for significant regressions within the 17 AMPs (after the exclusion of the 3 noisy maps, see Chapter 3, Section 3.2) and any mean maps that were significant would be loaded into Fsleys to visualize the significant amplitudes of interests.
3.3. Results

Correlations between the splits from the split-half study for an optimal dimension are reported. The discerned optimal dimensionality was then used to run PROFUMO to assess the neural correlates of state and trait depression using regression models. State models were run with and without the inclusion of Neuroticism.

3.3.1. Optimal dimension for running PROFUMO

Dimension 10 had a lower mean split-half spatial correlation (r=0.78) compared to 20 (r=0.83) & 30 (r=0.82), which may indicate that there are more than 10 networks in which the brain can be divided as seen in Table 7.

Table 7 Indicates the proportion of Similarity correlation between scans across both timepoints per dimension increasing from 10 to 50 increasing in increments of 10, with a binary cut-off at r=0.5 and r=0.95.

<table>
<thead>
<tr>
<th>Dimensions</th>
<th>Similarity Fraction</th>
<th>Proportion of Similar components (r=0.50)</th>
<th>Similarity Fraction</th>
<th>Proportion of Similar components (r=0.95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>7.8/ 10</td>
<td>0.78</td>
<td>2 / 10</td>
<td>0.20</td>
</tr>
<tr>
<td>20</td>
<td>16.5 / 20</td>
<td>0.83</td>
<td>11 / 20</td>
<td>0.55</td>
</tr>
<tr>
<td>30</td>
<td>24.7 / 30</td>
<td>0.82</td>
<td>12 / 30</td>
<td>0.40</td>
</tr>
<tr>
<td>40</td>
<td>31.3 / 40</td>
<td>0.78</td>
<td>17 / 40</td>
<td>0.43</td>
</tr>
<tr>
<td>50</td>
<td>35.5 / 50</td>
<td>0.71</td>
<td>14 / 50</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Additionally, the higher the dimensions from 10 to 50, the greater the dissimilarity, i.e., the less correlated the splits are. When completing a correlation between the two splits, dimension 20 has the greatest correlation with 83% of PROFUMO group maps being similar at a threshold of r=0.5 and 55% of PROFUMO group maps being similar at a threshold of r= 0.95 (see Figure 10 for visual representation). As such, dimension 20 will be used for future PROFUMO analyses herein.
Figure 10. Violin Plots for Split-half correlations across two timepoints at dimensions 10 to 50 increasing in increments of 10. The x-axis indicates the correlations between the split and the y-axis indicates the different dimensions tested.

More so, it is known that the use of higher dimensions relates to lower stability as they relate to smaller modes and thus fewer brain voxels being covered. Contrary to our expectation of lower dimensions producing better results, here we see the dimension of 10 has a lower correlation than 20 & 30, which indicates there are more than 10 networks in which the brain can be divided. Furthermore, the tails on the violin plot are indicative of components that capture group-level structured noise.

3.3.2. Removing noisy maps for statistical analyses

Through visual investigation of the brain maps, 3 out of the 20 modes were noisy, as such these were dropped, and everyone had 17 dimensions retained (see Figure 11). For all other signal components, refer to Appendix 6.4.
Figure 11. Group maps of noisy modes were excluded from analyses (modes 10, 13, 14). Color bar scale: red indicates positive elements of the network and green indicates negative elements of the network.

For each of the 193 individuals at each timepoint, there were 17 AMPs, 136 edges in the netmat, and 136 spatial overlap correlations. The 136 edges and spatial overlap correlations were calculated by taking the upper triangle from the 17x17 correlation matrix following the calculation of $17*(16)/2 = 136$ and subtracting one from the other at each timepoint. The 3 noisy maps were dropped from the 20 AMPs, resulting in 17 AMPs included in the analyses. Thereafter, multiple regression analyses were conducted to see the relationship between all regressors and the 3 PROFUMO measures described here, followed by multiple comparisons corrections using false discovery rate.

### 3.3.3. Differential neural correlates of state depression.

Results of the regression analyses inclusive of all 6 regressors (inclusive of neuroticism) on the 17-amplitudes after being corrected for multiple comparisons using false discovery rate (FDR) found that no amplitudes were significant in relation to a change in RDS over time. More so, the regression analyses for the 136 spatial overlap correlations also yielded no significant results in relation to RDS change over time after being corrected for multiple comparison using FDR. However, the regression analyses for netmat edges indicated a difference in RDS over time was significant for two netmats.

Of the two Netmat edges which passed the significance threshold the first corresponded to functional connectivity between the peripheral visual network and the default mode network ($R^2 = 0.073$, $t(1,5) = -2.435$, $p=0.016$), as seen in Fig 12(A). The second Netmat edges which passed the significance threshold corresponded to the functional
connectivity between the somatosensory network and the anterior default mode network ($R^2 = 0.061$, $t(1,5) = -2.587$, $p=0.044$) as seen in Figure 12(B). These results did not change when removing Neuroticism from the model. More so, the negative t statistics indicate those who have an increase in state depression, have a bigger reduction in the strength of the connectivity between the two networks seen in Figures 12A and 12B.

![Longitudinal changes in functional connectivity](image)

**Figure 12.** Longitudinal changes in functional connectivity were seen between the peripheral visual network and the default mode network (A) – areas of activity are seen in the DMN (in red) which is anticorrelated with areas of the SN (in blue) – and between somatosensory network and anterior default mode network (B) were significantly associated with changes in state depression. Both subfigures have the correlation plotted per RDS residual for the significant NetMat across the two timepoints. The x-axis pertains to the RDS residuals and the y-axis pertains to the significant netmat edge.

### 3.3.4. Differential neural correlates of trait depression.

The regression analyses for trait depression inclusive of all 4 regressors (i.e., Neuroticism, age, sex, head motion) excluding the RDS score was done at timepoint 1 and timepoint 2. From the 17-amplitudes after being corrected for multiple comparisons using FDR, no amplitudes were significant at either timepoint. The regression analyses for the 136 spatial overlap correlations also yielded the 2 being significant findings, at timepoint 1, and one of those was also significant at timepoint 2.
Of the two spatial overlap correlations that were significant, the first corresponded to spatial overlap between the spatial maps for the default mode network and salience network as seen in Figure 13 (A). However, this finding only passed the significance threshold at timepoint 1 (R² = 0.147, t(1,4)=2.247, p=0.026), but was only trend-level significant at timepoint 2 after FDR correction (R² = 0.147, t(1,4)= 2.247, p=0.065). The second significant finding corresponded to the spatial overlap between the spatial maps for the left frontoparietal network and the peripheral visual network as seen in Figure 13B, which were significant in both timepoint 1 (R² = 0.085, t(1,4)=3.715, p=0.000) and timepoint 2 (R² = 0.061, t(1,4)=2.946, p=0.004). The positive t statistics indicate those who have an increase in trait depression, had more spatial overlap between the two spatial maps seen in Figure 13A and 13B.

Figure 13. Spatial overlap between the default mode network and the salience network (A); areas of activity are seen in the DMN (in red) which is anticorrelated with areas of the SN (in blue) and the left frontoparietal network and peripheral visual network (B) were significantly associated with trait depression. Both subfigures have the correlation per trait for the significant spatial overlap correlation plotted per respective timepoint. The x-axis pertains to neuroticism at the respective and the y-axis pertains to the significant spatial overlap matrix.
3.4 Discussion and Significance

The study aimed to explore the neural correlates of state and trait depression by using various regression analyses. The results showed that for state depression, only two netmats edges passed the significance threshold after FDR correction. The first involved functional connectivity between the somatosensory network and the anterior default mode network (DMN), while the second involved functional connectivity between the peripheral visual network and the DMN. Both results revealed negative t statistics which indicated that those who had a bigger increase in state depression had a bigger reduction in the strength of connectivity between the two networks. For trait depression, the regression analyses for the 136 spatial overlap correlations yielded two significant results after FDR correction. One which was significant at both timepoints, exhibiting spatial overlap between the left frontoparietal network and peripheral visual network, whilst the second was significant at timepoint 1 and trend-level at timepoint 2 exhibiting spatial overlap between the DMN & SN. More so, both results revealed positive t statistics which indicated that those who had higher trait depression had more of an overlap between the two networks.

3.4.1. Differentiating between state- and trait- based depression using Netmat and Spatial maps PROFUMO outputs

The study’s main findings supported the hypotheses that PROFUMO netmats were significant for state-based depression whilst PROFUMO spatial overlap correlations between spatial maps were significant for trait-based depression. This is consistent with the hypothesis proposed in Chapter 3, Section 1.4.

For state-based depression, the hypotheses discussed indicated that netmat edges – which are related to the timeseries - are more dynamic and as such are expected to change with time. Consequently, the instability of timeseries in netmats compared to the spatial organization captured in spatial overlap matrices are consistent with views of why netmats are related to state-based depression. A meta-analysis of 9 studies by Delayeau and colleagues in 2010 investigated emotional activation to treatment effects on functional connectivity in the brain. They found hyperactivity in areas of the limbic &
paralimbic areas (involved in emotion, memory & motivation) and hypoactivity in the neocortical areas (involved in higher cognitive functions – conscious thought, perception, sensory processing, language) were both reversed after depressed patients were given an antidepressant. This study is in line with the idea that regional fMRI timeseries track state-based depression, as the antidepressants were able to modulate the activity within these brain areas.

It is important to note that the pairs of networks that were significant in state and trait depression occurred between association and sensorimotor networks. Sensorimotor networks process and integrate sensory information within a specific modality, whereas association networks integrate information across multiple sensory modalities and cognitive domains (Mesulam, 1998). Research has indicated that sensorimotor networks tend to exhibit fewer specializations compared to association networks (Bassett et al., 2008). The results indicate connectivity between association and sensorimotor networks may allow for integration and coordination of information processing across different domains of cognitive and sensory processing such that connectivity between these two types of networks could be important in the manifestation of both state and trait depression.

Thus, these differential PROFUMO neural correlates could have important implications for distinguishing between transient and stable depression, and in turn implications for treatment selection and prognosis. By understanding the neural correlates of state-based depression, more targeted interventions that focus on modulating dynamic functional connectivity could be developed. Overall, the use of both Netmats and spatial maps could provide clinicians with a valuable tool for accurately diagnosing and treating depression. These findings have implications for diagnosis and treatment approaches.

3.4.2. The role of sensorimotor networks in depression

Research into the neural correlates of depression usually considers association networks that process a variety of cognitive functions such as the DMN and the SN. Contrary to the hypotheses, our findings highlight the role of functional connectivity between the association and sensorimotor networks specifically the visual and
somatosensory networks in state and trait depression. Although rarely discussed, some previous research has investigated the role of the visual cortex in the malfunction of depressive disorders. In 2023, Wu, Lu & Zhang, reported frequency specific changes and decreased degree of centrality in the occipital lobe of MDD patients using rs-fMRI when compared to controls. More so, research has examined the role of the somatosensory cortex in emotional regulation, and found that structural and functional changes in the somatosensory cortex of individuals with mood disorders, indicating its involvement and potential suitability for treatment targeting for emotional health disorders such as depression (Kropf et al., 2019). Another study by Kang and colleagues in 2018 also reported that functional connectivity between the somatosensory cortex and thalamus was abnormal and associated with core clinical symptoms in depression. Both the visual cortex and somatosensory network have been linked to arousal, which has been found to be dysregulated in depression (Bijsterbosch et al., 2018; Wong et al., 2013).

One explanation for the involvement of these sensorimotor networks in depression can be inferred from arousal effects – which refer to a change in levels of alertness and excitement which have been reported as dysregulated in depression (Joormann & Gotlib, 2010). In 2014, Hegerl & Hensch proposed the vigilance regulation model of affective disorders which proposes that affective disorders are caused by dysregulation of the brain’s vigilance system that is responsible for regulating arousal, attention, and autoregulatory behavior in response to environmental stimuli. This contrasts with the arousal regulation model which suggests that affective disorders are caused by dysregulation of the brain’s arousal system, which is responsible for regulating wakefulness and sleep. The arousal regulation model of affective disorders (Thase & Howland, 1995; Harvey, 2002; Clark et al., 1991) suggests that a major aspect in the development of depression is the inability to regulate arousal levels. According to the model, individuals with affective disorders may have heightened or decreased sensitivity to environmental cues, leading to maladaptive responses (e.g., rumination, avoidance, impulsivity). These aspects of attention regulation and hyperactivity are more closely related to the vigilance regulated model. More broadly, research has looked into the regulation of arousal as a response predictor for antidepressant therapy in depression as the model suggests that regulating arousal levels could be an important aspect of treating depression (Schmidt et al., 2017). In their paper, Schimdt and
colleagues found a higher level of brain arousal in those who responded to antidepressant medication, which supports the idea that dysregulation of brain arousal is a possible predictor of treatment response in affective disorders. The vigilance regulation model aligns with the findings that implicate sensorimotor networks such as the visual cortex and somatosensory cortex in depression as there could be parallels between affective disorders and conditions such as attention-deficit/hyperactivity disorder which are characterized by deficits in attentional control and hyperactivity. More so, studies into arousal indicate that an increase or decrease in sleep are both known symptoms of depression and various arousal statistics through fMRI and electroencephalogram (EEG) research have been linked to connectivity in the visual cortex and this suggests that sleep might mediate this association (Horovitz et al. 2008; Wong et al., 2013). Thus, this result indicates the importance of considering sensory processing disruption and arousal regulation in understanding and treating depression.

Additionally, developmental dependencies along the association-sensorimotor networks axis may play a role in the link between sensorimotor networks and depression. The DMN is involved in self-referential processes and internal thoughts, while the sensorimotor networks are involved in sensory processing. Kong et al. (2021) studied the role of sensory-motor cortices in shaping the dynamic functional connectivity of the human brain and found that sensory-motor regions serve as critical hubs for the integration of information across multiple functional networks and modulate the strength and directionality of inter-network interactions. Dysfunctions in the connectivity between these regions have been associated with depression as seen in Pines et al. (2022) where they examined the developmental trajectories of personalized brain networks using a longitudinal dataset and found that the development of large-scale networks and subnetworks are dissociable, with different patterns of maturation across different scales of organization.

Another hypothesis that could explain the involvement of these sensorimotor networks comes from research which suggests somatic symptoms experienced by individuals with depression may involve the somatosensory network. Individuals who exhibit depression report psychomotor slowing (Buyukdura, McClintock & Croakin, 2013) and reduced reaction time (Gale Harris & Deary, 2016) which might explain the associations with the
somatosensory networks as reduced reaction time and increased restlessness are symptoms of depression. A study by Paquet and colleagues (2022) evaluated the feasibility of standardized psychomotor examinations for patients with depression. They found that depressed patients exhibited significant differences from healthy controls in psychomotor symptomatology characterized by specific abnormalities in muscle tone, body image, motor skills, and rhythmic adaptation. Thus, results in this study in conjunction with the literature point to the idea that somatic symptoms in depression extend beyond psychomotor retardation to involve aspects of motor and bodily functions which may implicate these sensorimotor networks.

Lastly, it is important to note that the confounds such as head motion may also have affected the findings. Previous studies have shown that head motion can impact functional connectivity results with head motion being associated with decreased functional coupling in the DMN & FPN (Van Dijk, Sabuncu, Buncker., 2012). However, head motion was included as a confounding variable in all of our analyses so it is unlikely that head motion explained our findings.

3.5. Significance, Limitations, and Future Direction

3.5.1. Significance

This is the first study to differentiate neural correlates of state and trait depression using PROFUMO. The results indicate that netmats and spatial overlaps are differential correlates for state and trait depression, respectively, which could have implications for diagnosis and treatment. Furthermore, the most significant result was the involvement of sensorimotor networks in trait and state level depression. The results of this study highlight the importance of investigating the role of sensorimotor networks in the development and maintenance of depression, and their potential as targets for therapeutic interventions.

3.5.2. Limitations
Although this study benefited from several strengths including the availability of longitudinal data to dissociate state and trait depression to then discern the neural correlates depression, as well as enabling the cumulative scoring and the repeated data to enable replication efforts, multiple limitations are worth noting. The first limitation was the small sample size of the study which arose due to the focus on individuals with a large longitudinal change in depression – due to the need to achieve the desired dissociation between state and trait depression. The second limitation was that the research focused on size-dependent changes to ensure the neural correlates of depression were being investigated. It is possible that larger effects might be observed in a group comparison between individuals with a longitudinal change versus individuals with no change. The third limitation is that within the trait results, state was not controlled for due to the high cross-sectional correlation, which reduced the interpretability of trait findings as independent of state depression.

### 3.5.3. Future Direction

The limitations discussed in Section 5.2. of this chapter are addressed in a new study planned by members of the Personomics research group. The plans for this new study are proposed in a registered report, currently under review at Nature Human Behavior. In the report, the limitation of the sample size is addressed by adding participants from the most recent release from the UK Biobank. More so, to increase statistical power, the report compares those who experience large changes and no changes for the state analyses. Lastly, to control for state depression in the trait level analyses, a high and a low trait depression group are defined which are both low in state depression to allow for a full dissociation. Thus, this registered report aims to build upon these findings in this chapter and incorporate all such changes for the prospective study.

Additionally, the findings highlight the importance of investigating the role of sensorimotor networks in the development and maintenance of depression and their potential as targets for therapeutic interventions. Prospective summer students within the Personomic research group will test the different hypotheses discussed in section 3.4 of this chapter to discern the role of sensorimotor networks in depression.
Chapter 4: Is there an overlap in the PROFUMO correlates of life events & depression

Life events such as hassling events can lead to feelings of hopelessness, helplessness, and a lack of control over one’s life that can result in the onset of depression. Uplifting events, however, can help individuals to cope with stressful life events and prevent the development of depression. Research into the correlates of a group of life events and their correlates is limited, thus research into the overlapping correlates of life events and depression is sparse. This chapter begins by reviewing existing literature on hassles and uplifts, followed by the parallels between the allostatic load model of depression and its impact on physiological systems including the brain; which provide a potential explanation for the existence of possible overlapping correlates of life events and hassles. The chapter covers a study which investigates if there is an overlap between the PROFUMO neural correlates of life events and depression. The study uses the same methodology seen in Chapter 3 to discern the neural correlates of life events and depression. The study uses PROFUMO and ascertains if there is an overlap with the neural correlates of depression found in Chapter 3. These results and their significance are discussed.

4.1. Background and Motivation

4.1.1. The distress-continuum, disorder-threshold model of depression (Wahid et al., 2021)

The distress-continuum, disorder-threshold model is a framework for understanding depression that proposes that depression is a continuum that ranges from normal levels
of distress to the threshold for clinical disorder (Figure 14) – for details on the model refer back to Chapter 2, Section 1.2.

![Figure 14. The distress-continuum, disorder-threshold model of depression (From Wahid et al., 2021).](image)

This model of depression suggests that depression occurs along a continuum of distress, where individuals experiencing higher levels of distress are more likely to develop depression. At the same time, there is a threshold beyond which an individual's symptoms become severe enough to be classified as a depressive disorder. This model implies that hassles can contribute to increased distress, and potentially increase the risk of depression, while uplifts can help reduce distress and potentially protect against the development of depression. Hassling events can accumulate over time and contribute to an individual’s overall level of distress. This ongoing distress can eventually surpass the disorder threshold, leading to the development of clinical depression. For example, an individual experiencing chronic financial strain or relationship issues may accumulate a significant amount of distress, increasing the likelihood of developing depression. In this sense, hassles may act as a risk factor for depression, contributing to the development of the disorder in vulnerable individuals. On the other hand, uplifts, such as positive life experiences and events, can help reduce distress and potentially protect against the development of depression. These positive experiences may help individuals to build
resilience and buffer against the negative impact of stressors. For example, an individual who experiences positive social support from friends and family may be better able to cope with ongoing stressors, reducing their overall level of distress and potentially protecting against depression. Furthermore, uplifts may have a unique impact on neural correlates of depression, potentially even reducing the risk of developing depression. Research has shown that positive experiences can lead to changes in brain structure and function, including increased activity in regions associated with positive affect and decreased activity in regions associated with negative affect. This suggests that uplifts may have a protective effect on the brain and potentially reduce the risk of developing depression. In Chapter 2, the relationship between depression and both hassles and uplifts were established, which could inform the development of targeted interventions aimed at reducing risk factors and promoting protective factors for depression.

4.1.2. Overlapping resting state networks for depression and life events

Some studies have investigated the neural correlates of specific classes of hassles. For example, a study by Butterworth & Colleagues in 2012 investigated whether middle-aged adults currently experiencing financial hardship had detectable brain differences from those who have not experienced such adversity. They were able to show that adults who reported financial hardship had smaller left and right hippocampal and amygdalar volumes compared to those who did not report any hardship. As both the hippocampus and amygdala are part of the DMN, these findings may suggest the involvement of rs-fMRI networks of the DMN. Additionally, no relationship was found between hardship and intra-cranial volume or any of the volumetric measures. Despite the pathophysiological mechanisms mediating the effect of hardship on brain structure and cognition are unclear, financial hardship can be considered as a potent stressor, and this result is consistent with the view that hardship influences hippocampal and amygdalar volumes through hypothalamic–pituitary–adrenal axis function and other stress-related pathways (Juneja et al., 2002; Dowd et al., 2009).

Despite the lack of research into the resting state neural correlates of hassles, research has shown that people with depression have a stronger memory for negative occurrences when compared to those without depression, with greater activity in the
amygdala (Ramel et al., 2007; Hamilton & Gotlib, 2008). More so, a study by Foland-Ross and colleagues in 2014 found that changes in depression over 18 months were linked to rs-fMRI activity in the PCC & medial prefrontal cortex when participants viewed negative images suggesting that the brain's reaction to negative/hassling events may be a better predictor of the course of depression overtime, compared to the memory for negative/hassling events (Foland-Ross et al., 2014). However, there is a lack of work on the neural correlates of the cumulative impact of suffering from a range of hassles. This study aims to address this gap by identifying the neural correlates of the hassle, using the hassles summary score developed in Chapter 2, Section 2.4.

When considering uplifts, the only group of uplifts consistently investigated is physical activity levels. Zhang et al., 2022 found that connectivity strength and amplitude of the DMN, SN, and CEN were both associated with mental health and physical activity. Previous research has reported that engaging in physical activity can have a positive effect on mental health by reducing symptoms of negative mood (Anderson et al., 2013). These benefits also translate to resting state functional connectivity between the DMN and within the CEN, when individuals aerobically walked for over a year (Voss et al., 2010), and partook in several sessions of high-intensity interval training (Greeley et al., 2021), respectively. Furthermore, studies investigating the impact of greater subjective well-being (in the sense of hedonic pleasure - striving to feel enjoyment and comfort) have found weaker connections between the SN and anterior DMN as well as the DMN and FPN (Shi et al., 2018). These findings indicate that those with higher subjective well-being have more flexible and adaptive rs-fMRI networks involved in self-reflection, emotional regulations, and cognitive control. Taken together, these examples indicate increased activity within DMN, SN, FPN, and CEN may have a protective effect against hassling events and the subsequent progression of depression.

Depression itself is a complex disorder, and as seen in Chapter 1 Section 3.1, the meta-analysis of 36 rs-fMRI studies into depression by Mulder and colleagues in 2015 reported alternations in connectivity of several RSNs such as the default mode and salience networks. Another meta-analysis of 25 rs-fMRI studies into depression reported alternations in the connectivity of several RSNs such as the SN, DMN, FPN, and CEN (Kaiser et al., 2015). Although a comparison of the existing literature suggests that similar networks may be involved in hassles/uplifts and depression, direct analytical
comparisons are lacking. This study will address this gap in the literature by elucidating the neural correlates of cumulative hassles and cumulative uplifts and then comparing the overlap of results with the neural correlates of depression (as established in Chapter 3).

4.2. Methods

The same subjects from Chapter 3 were used within the study, as well as the same PROFUMO outputs. Thus, regression analyses were used to discern neural correlates of hassling and uplifting life events, whilst controlling for confounds. Next, significant PROFUMO outputs was inspected to discern what brain networks were involved. Lastly, the comparison was conducted between the significant networks for depression as reported in Chapter 3 Section 3.2 and Section 3.4.

4.2.1. Dataset

To enable direct comparisons between neural correlates of hassles/uplifts and neural correlates of depression, the same 193 individuals who had imaging (from Aim 2) and life event data (from Aim 1) across both timepoints were retained for this study.

4.2.2. PROFUMO Output

The same PROFUMO outputs (as discussed Chapter 3, section 2.4) were used to discern the neural correlates of life events (as discussed in Chapter 2). These includes amplitudes (AMPs) which indicate the signal strength of a mode (i.e., how strong that network is for each individual). Next was Netmats which is the connectivity matrix that takes the timeseries from 2 modes and computes a correlation between them. The final output is a spatial overlap matrix that explains the degree of spatial organization between the different spatial maps (which explains the spatial layout within a mode) using the correlations computed. Thus, to assess the neural correlates of depression these PROFUMO outputs can be used as targets in the regression model.
4.2.2. Statistical model for the association between PROFUMO and life events

Out of the 193 individuals, only 11 had a change in hassles and 7 had a change in uplifts across the two timepoints. Therefore, a cross-sectional approach was taken to discern the PROFUMO correlates of hassles and uplifts. More so, due to their collinearity (r=-0.77) separate analyses were performed for hassle and uplift at each timepoint. Regressors of interest included the cumulative hassle score or the cumulative uplift score (as derived in Chapter 2, section 2.5). All models were controlled for current depression (as assessed by RDS-4), their age at the respective timepoint, gender, and head motion at each timepoint. To assess the relationship between life events and PROFUMO measures of interest the following models were run as seen in 4.1 and 4.2. Given that data was available at another timepoint, the analyses were repeated at timepoint, the analyses were repeated at timepoint 2. Prior to inclusion in the regression analysis, all regressors were z-scored (for the PROFUMO spatial overlap correlation, a Fisher's r-to-z transformation was conducted) to standardize their scales and make them comparable in terms of their unit measurement.

\[ Y = \beta_0 + \beta_1 X_1 + \beta_2 X_3 + \beta_4 X_4 + \beta_5 X_5. \]  \hspace{1cm} (4.1)

\[ Y = \beta_0 + \beta_1 X_2 + \beta_2 X_3 + \beta_4 X_4 + \beta_5 X_5. \]  \hspace{1cm} (4.2)

Where \( Y \) = PROFUMO measures of interest (Amplitude, NetMats, and Spatial Correlation Matrix), \( \beta_0 \) = the intercept, \( X_1 = \) Hassles, \( X_2 = \) Uplifts, \( X_3 = \) Age at relevant timepoint, \( X_4 = \) Sex, \( X_5 = \) Head motion at relevant timepoint.

4.2.3. Statistical model for assessing the overlap between correlates of life events and depression: conjunction analyses

Upon discerning the neural correlates of hassles and uplifts, two conjunction analyses were run between the results from Chapter 4, Section 2.2. and those from Chapter 3 to discern if there are any overlaps in PROFUMO correlates of trait depression and hassles or uplift. Trait depression was focused upon as these analyses were also cross-sectional and therefore matched the approach for determining the neural correlates of
hassles/uplifts. The conjunction analysis (Friston et al., 1999) will be repeated using findings from timepoint 2, to assess the robustness of the findings. The goal of a conjunction analysis is to find the PROFUMO features that pass FDR corrected significance threshold across multiple analyses.

4.3. Results

4.3.1. PROFUMO correlates of hassling life events

Results of the regression analysis inclusive of all 4 regressors on the 17 amplitudes after being corrected for multiple comparisons using false discovery rate (FDR) at both timepoint and timepoint 2 found that no amplitudes were significant in relation to hassles. More so, the regression analyses for 136 netmat edges also yielded no significant results in relation to hassles after being corrected for multiple comparisons using FDR. However, regression analyses for the 136 spatial overlap correlations after multiple comparison corrections indicated 3 significant spatial overlap correlations at both timepoints as seen in Table 8.

Table 8 Presents regression results for hassles at both timepoints. Here, the PROFUMO output of spatial overlap matrices survived multiple comparison correction via FDR. Results include: t statistics and significance level (findings with p < 0.05 are marked with *). Rows highlighted in grey indicate spatial overlap findings that were significant in the regression analyses across both timepoints.

<table>
<thead>
<tr>
<th>Dimensions</th>
<th>Spatial Overlap Correlations</th>
<th>Timepoint 1 result hassles</th>
<th>Timepoint 2 result hassles</th>
</tr>
</thead>
<tbody>
<tr>
<td>0,16</td>
<td>13</td>
<td>t(6,187)=-2.609, p=0.075</td>
<td>t(6,187)=-2.609, p=0.010*</td>
</tr>
<tr>
<td>3,0</td>
<td>51</td>
<td>t(6,187)=-2.695, p=0.008*</td>
<td>t(6,187)=-2.858, p=0.005*</td>
</tr>
<tr>
<td>3,17</td>
<td>65</td>
<td>t(6,187)=-2.896, p=0.004*</td>
<td>t(6,187)=-3.063, p=0.003*</td>
</tr>
<tr>
<td>6,15</td>
<td>114</td>
<td>t(6,187)=-0.736, p=0.044*</td>
<td>t(6,187)=-0.736, p=0.079</td>
</tr>
<tr>
<td>7,1</td>
<td>120</td>
<td>t(6,187)=-3.462, p=0.001*</td>
<td>t(6,187)=-3.541, p=0.001*</td>
</tr>
</tbody>
</table>

The first results for hassles involved the spatial overlap between the spatial maps for the salience network and the left frontoparietal network as seen in Figure 15 (A). The second results for hassles involved the spatial overlap between the spatial maps for the
somatosensory network and the left frontoparietal network Figure 15(B). The last result for hassles involved the spatial overlap between the spatial maps for the peripheral visual network and anterior DMN as seen in Figure 15(C).

Figure 15. Spatial overlap findings that were significantly associated with cumulative hassles included overlap between the salience network and the left frontoparietal (A), overlap between the somatosensory network and the left frontoparietal (B), and overlap between the peripheral visual network and anterior DMN (C). Both subfigures have the correlation per cumulative hassle score for the significant spatial overlap correlation plotted per respective timepoint.

4.3.2. PROFUMO correlates of uplifting life events

Results of the regression analyses inclusive of all 5 regressors on the 17 amplitudes after being corrected for multiple comparisons using FDR at both timepoints found that no correlates were significant in relation to uplifts. However, the regression analyses for 136 netmat edges indicated two netmat edges and three spatial overlap matrices were significant for uplifts at both timepoints, Table 9.
Table 9 Presents regressions results for uplifts at both timepoints. Here, the PROFUMO output of Netmats survived multiple comparison correction via FDR. Results include: model $R^2$ value, $t$ statistics and significance level, $p < 0.05$. Rows highlighted in grey indicate netmat edges which were significant in the regression analyses across both timepoints.

<table>
<thead>
<tr>
<th>Dimensions</th>
<th>Netmats</th>
<th>Timepoint 1 result uplifts</th>
<th>Timepoint 2 result uplifts</th>
</tr>
</thead>
<tbody>
<tr>
<td>6,4</td>
<td>74</td>
<td>$t(6,187)=3.014, p=0.003^*$</td>
<td>$t(6,187)=3.162, p=0.002^*$</td>
</tr>
<tr>
<td>8,5</td>
<td>93</td>
<td>$t(6,187)=2.695, p=0.041^*$</td>
<td>$t(6,187)=2.778, p=0.072$</td>
</tr>
<tr>
<td>5,6</td>
<td>107</td>
<td>$t(6,187)=3.561, p=0.000^*$</td>
<td>$t(6,187)=3.176, p=0.002^*$</td>
</tr>
</tbody>
</table>

Of the two Netmats which passed the significance threshold the first corresponded to the functional connectivity between the posterior default mode network and the central visual network, as seen Figure 16(A). The second corresponded to the functional connectivity between the visual medial network and central visual network, as seen Figure 16(B).

![Functional Connectivity](image)

**Significant at both timepoints:** T1: $t(6,187)=3.014, p=0.003$, T2: $t(6,187)=3.162, p=0.002$.

Figure 16. Indicates functional connectivity between two pairs of networks associated with uplifts. The first involved functional connectivity between the posterior default mode network and the central visual network (A) and the second involved functional connectivity between the visual medial network and the central visual network (B). Both subfigures have the correlation per cumulative uplift score for the significant netmat plotted per respective timepoint.
The regression analyses for the 136 spatial overlap correlations also yielded three significant correlates that were significant at both timepoints after being corrected for multiple comparisons using FDR as seen in Table 10.

Table 10 Presents uplift regressions results for the PROFUMO output of spatial maps which survived multiple comparison corrections via FDR. Matrices at both timepoints. Results include: t statistics and significance level, p < 0.05. Rows highlighted in grey indicate spatial maps which were significant in the regression analyses across both timepoint.

<table>
<thead>
<tr>
<th>Dimensions</th>
<th>Spatial Overlap Correlation</th>
<th>Timepoint 1 result uplifts</th>
<th>Timepoint 2 result uplifts</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,17</td>
<td>31</td>
<td>t(6,187)=3.073, p=0.002*</td>
<td>t(6,187)=3.196, p=0.002*</td>
</tr>
<tr>
<td>1,18</td>
<td>32</td>
<td>t(6,187)=2.964, p=0.003</td>
<td>t(6,187)=2.964, p=0.003*</td>
</tr>
<tr>
<td>4,1</td>
<td>69</td>
<td>t(6,187)=2.778, p=0.006*</td>
<td>t(6,187)=2.413, p=0.071</td>
</tr>
<tr>
<td>7,1</td>
<td>120</td>
<td>t(6,187)=3.924, p=0.000*</td>
<td>t(6,187)=3.541, p=0.001*</td>
</tr>
</tbody>
</table>

Of the three spatial overlap correlations which passed the significance threshold for uplifts, the first corresponded to functional connectivity between the spatial maps for the peripheral visual network and the somatosensory network as seen in Figure 17 (A). The second result corresponded to functional connectivity between the spatial maps for the peripheral visual network and the anterior DMN Figure 17 (B). The third corresponded to functional connectivity between the spatial maps for the peripheral visual network and the DMN Figure 17 (C).
Figure 17. Spatial overlap findings that were significantly associated with cumulative uplifts included overlap between the peripheral visual network and the somatosensory network (A), overlap between the peripheral visual network and the anterior DMN (B), and overlap between the peripheral visual network and the DMN (C). Both subfigures have the correlation per cumulative uplift score for the significant spatial overlap correlation plotted per respective timepoint.

4.3.4. Overlapping PROFUMO correlates

When assessing the overlap between the neural correlates of life events and depression the results of the conjunction analyses as seen in Figure 18 indicate no overlap between correlates of life events and trait depression.

Figure 18. Summary of significant PROFUMO correlates for depression and life events.
However, when assessing the neural correlates of life events, only netmats presented significantly for uplifts, whilst spatial overlap correlations were significant for both types of life events. More so, the same two networks: the peripheral visual and the anterior default mode network both survived multiple comparison corrections for both types of life events across both timepoints.

4.4. Discussion and Significance

The two aims of this study were to determine the neural correlates of cumulative hassles and cumulative uplifts and to establish whether the neural correlates of hassles and uplifts overlap with the neural correlates of depression. Regarding the first aim, the study indicated that cumulative hassles were associated with spatial overlap between three networks: 1) left-FPN & SN, 2) a-DMN & peripheral visual network, and 3) the left-FPN & the somatosensory network. Cumulative uplifts were associated with both spatial overlap and functional connectivity. Spatial overlap was significant between the peripheral visual network and three other networks (a-DMN, DMN, and somatosensory network). Whereas, functional connectivity was significant between the central visual network and two other networks (p-DMN and the visual medial network). Regarding the second aim, the results revealed a lack of overlap in the neural correlates of depression and hassles/uplifts.

4.4.1. Many networks contribute to the neural correlates of hassles & uplifts

The results indicate many of the networks found to contribute to hassles/uplifts included the expected association networks (DMN, SN, and FPN) along with unexpected sensorimotor networks (visual and somatosensory). The DMN was also implicated in both life events. Research has shown that the DMN has been active during self-referential processing in response to negative emotional stimuli (hassling events) compared to neutral stimuli (Sheline et al., 2009; Wagner et al., 2015). The authors also reported greater BOLD activation in the amygdala and hippocampal complex for a hassling event which they stated could be explained by depressed patients being unable to down-regulate activity mainly within the DMN. However, recently some studies have also
shown how the DMN has been involved in the processing of reward-related stimuli through its involvement in self-referential and social cognition tasks (Dobryakova & Smith, 2022). As such, when an individual experience uplifts, they may engage in self-reflection, positive talk, and social interaction that activates the DMN (Dohmatob, Dumas & Bzdok, 2020). These results also indicate that the DMN is not explicitly seen in either hassling or uplifting events, and this could be due to the brain’s highly individualized response to different emotional stimuli. Contrary to the hypothesis, the SN was only seen for hassles and not uplifts, which is in line with the literature which suggests the network is more active in response to negative emotional stimuli (hassles) compared to positive emotional stimuli (uplifts) (Lee et al., 2014), whilst other studies have reported fewer connections within the salience network for those who experience higher levels of positive feelings (Qi et al., 2021). More so, key regions within the SN such as the dorsal anterior cingulate cortex are reported to be associated with conflict regardless of emotional stimulus (Duggirala et al., 2022) – a region seen to be active for trait depression. Nonetheless, it is important to note that SN activity is not solely determined by the emotional valence of the stimuli and these results suggest the SN is not a key network when considering uplifting life events. Although the hypotheses expected the involvement of the DMN & SN, they did not take into consideration the involvement of the FPN or the somatosensory network – which were implicated in the neural correlates of trait-level depression. Previous research has, however, implicated the frontoparietal network in hassling life events, where a study reported psychosocial stress selectively impairs attentional control and disrupts functional connectivity within a frontoparietal network that mediates attention shifts (Liston, McEwen & Casey, 2009). More so, research has also shown that functional alteration of the somatosensory network has been reportedly induced by early-life stress (Takatsuru & Kobuchi, 2015) so these results show this is likely still the case for late-life stress. When considering the visual cortex, results implicated it was implicated in both life events.

Additionally, the neural correlates of cumulative uplifts were associated with functional connectivity and network overlap for visual networks which are primarily responsible for processing visual information from the environment, visual perception, object recognition, and spatial awareness. One possible reason for why the visual cortex was involved stems from the idea of positive attentional bias in which uplifting events could
increase positive attention bias (i.e., such that one focuses more on positive events) combatting depression which is characterized by negative attentional bias (i.e., where one focuses more on negative events). Some research suggests that the visual network may be more likely to respond to the valence of visual stimuli rather than the emotional content of the stimuli (Gerdes et al., 2010) and is thus influenced by individual differences in personality and emotion regulation which could impact the extent to which someone employs a positive attentional bias (Bendall et al., 2022). However, the activity of the visual cortex can also be influenced by individual differences in personality and emotion regulation. Parkinson, Kornelsen, and Smith (2019) found that higher levels of trait mindfulness showed decreased activity in the visual cortex in response to negative emotional stimuli compared to individuals with lower levels of trait mindfulness. Furthermore, visual imagery – which is an effective technique for regulating emotions and visual networks, has been implicated in producing and manipulating visual images used to regulate emotions (Holmes & Mathews, 2010). Support for this explanation is seen in work from Kosslyn et al. (1991) where the visual cortex was shown to be involved in generating mental images, and Fusar-Poli et al. (2009) reported that the visual cortex was implicated in regulating emotions in response to visual stimuli. Overall, while the visual cortex may be more likely to respond to the valence of visual stimuli rather than the emotional content of the stimuli and individual differences in personality and emotion regulation can also play a role in determining its activity, which may explain its presence for both hassles and uplifts.

4.4.2. Spatial overlap between the peripheral visual network and the anterior DMN was linked to both hassles and uplifts.

One possible explanation for the overlap between the visual network and the DMN could be the role of the DMN in visual processing in self-referential processing (Sheline et al., 2009) and autobiographical memory retrieval (Philippi et al, 2014; Northoff et al., 2006; Svoboda, McKinnon & Levine., 2006). Consequently, it is likely that the visual network may be involved in providing the visual information necessary for these processes. Another explanation stems from the overlapping function of the visual network and DMN in the role of visual imagery in emotion regulation (Sripada et al., 2014; Sambuco, Bradley & Lang., 2022), as the visual cortex is involved in generating mental images and
regulating the emotional response to visual stimuli (Kosslyn et al., 1991; Fusar-Poli et al., 2009). The DMN is reported to be involved in multisensory integration (Grady et al., 2006), whilst the visual network would be involved in the processing of visual information. Thus, it is possible that these two networks work together to integrate information from different sensory modalities to create a coherent representation of the environment. More so, several studies have shown that the visual network and DMN are functionally connected during rest, which may reflect the ongoing integration of sensory information with the self-referential process during rest (Raichle et al., 2001; Deco et al., 2013; Mantini et al., 2007). However, this study indicates that the degree of overlap varies across people as a function of the degree of hassles and uplifts experience. More specifically, the anterior DMN is more involved in integration, planning, and control functions, which are mostly conscious and are reciprocally related to dopaminergic reward processes (Knyazev, 2013). The peripheral visual network helps us gather information from the edges of our visual field, allowing us to be aware of our surroundings and respond to potential threats or relevant stimuli. It contributes to our spatial awareness, motion perception, and detection of objects or events that occur outside our direct line of sight (Lachenmayr, 2006). However, the connection between the two networks decreased the greater the number of hassles experienced and, this could indicate that the processing or integration of visual information from the periphery is affected or disrupted in the presence of more hassles. On the other hand, the connection between the two networks increased the greater the number of uplifts which suggests that a greater number of positive events may enhance the processing or integration of visual information from the periphery. These findings imply that the functional relationship between the peripheral visual network and the anterior DMN is modulated by the experience of hassles and uplifts. It suggests that the network connection between visual processing and cognitive control functions may be influenced by the emotional or rewarding context of an individual's experiences. This result may point to the complex interplay between visual processing, self-referential processing, ongoing sensory integration, and emotion regulation. Furthermore, it is possible that these two networks (visual and DMN) may be functionally and anatomically linked. However, further research is needed to confirm these hypotheses and fully understand the mechanisms underlying the observed spatial overlap between these networks.
4.4.3. No evidence of shared neural correlates between trait depression and either hassles or uplifts

There was no evidence of shared neural correlates between trait depression and hassles/uplifts as seen in Figure 17. One possible explanation for this result is that shared neural correlates of trait-depression and life events exist, but they are sub-threshold. However, when conducting correlations between un-thresholded t-statistics, they were low (R<0.1) which confirmed that there was no evidence for shared brain correlates between hassles or uplifts and trait-depression in this sample. It is possible that the relationship between life events and depression is mediated by other factors or indirect pathways such as inflammation, stress reactivity, or other psychological processes that are not captured by PROFUMO. Several studies into the relationship between life events and depression have found it to be complicated and multifaceted. Hammen et al. (2000) found that the relationship between life events and depression was moderated by cognitive vulnerability factors, with those exhibiting higher levels of cognitive vulnerability being more likely to experience depression in response to negative life events. Liu and Alloy (2010) reported that the relationship between life events and depression was mediated by negative cognitive styles, such as hopelessness and rumination, which are thought to contribute to the development and maintenance of depressive symptoms (Zhou et al., 2013). Kendler and colleagues (1999) discovered that the relationship between life events and depression was moderated by genetic factors, where those with a genetic vulnerability to depression were more likely to experience depression in response to negative life events.

There is also a substantial amount of research into the relationship between stress, the hypothalamic-pituitary-adrenal (HPA) axis, inflammation, and depression. Miller et al. (2011) reported that those who experienced higher levels of childhood adversity had elevated levels of inflammation, along with greater activation of the HPA axis and more negative emotional states in response to stressors. More so, research has also shown that chronic stress can lead to dysregulation of the HPA axis, which in turn can lead to increased inflammation and changes in neural function (McEwen, 2007; Pace & Heim, 2011). All these changes listed here lead to the development of depressive symptoms.
Other research has also shown that coping strategies and social support can be important safeguards against the negative effects of stress and life events in relation to depression (Cohen & Wills, 1985; Lazarus & Folkman, 1984). Pearlin et al. (1981) reported how social support was associated with lower depression levels among those who experienced high levels of stress. Taken together, there is a large body of research suggesting that the relationship between life events, stress, inflammation, and trait depression is complex and multifaceted.

4.5. Significance, Limitations and Future Direction

The current study indicates that many networks contribute to the neural correlates of hassles and uplifts, with spatial overlap between the visual network and DMN being linked to both groups of life events. However, contrary to the hypotheses, there was no evidence to support an overlap between neural correlates of depression and life events within this dataset using PROFUMO.

4.5.1. Significance

This is the first study to explicitly investigate the neural correlates of cumulative hassles and uplifts. The current study provides evidence for the involvement of several networks in hassles and uplifts. More so, uplifts were associated with functional connectivity and network overlap for visual networks which points to the idea of attentional bias also noted in Chapter 3 for depression (however in that case it was negative, and in this case, it was positive) indicating a possible counteraction to depression through activity within the visual cortex showing the balance of fluctuations in the ability to filter and inhibit irrelevant and/or emotionally valent visual input.

4.5.2. Limitations

Although this study benefited from several strengths including the availability of multiple domains of hassles/uplifts enabling the cumulative scoring and the repeated data to enable replication efforts, multiple limitations are worth noting. The first
includes the fact that the sample selected matched that used in Chapter 3 to enable the conjunction analyses. However, this sample may not be optimal for research into hassles/uplifts. The second limitation is that the analyses were performed at the network-level to focus on large-scale systems such as the DMN and the SN as opposed to smaller individual brain regions. As such, it is possible that shared neural correlates exist but at a smaller-scale regional level. The third limitation was that state depression may have an overlap with life events, however as only 11 individuals had a change in hassle and 7 individuals had a change in uplifts, this sample did not allow for a longitudinal analysis of life events to be conducted, which would have enabled a comparison against the longitudinal state depression analyses in chapter 3.

4.5.3. Future Direction

Future work may wish to study potential shared correlates in a sample specifically enriched for hassles/uplifts, and may wish to include resting state features at a regional level. More so, a larger sample or indeed the whole sample should be used to maximize power when investigating the neural correlates of life events. Additionally, a sample that has a population that experienced changes in life events longitudinally would be required to compare the neural correlates of longitudinal changes in life events to the neural correlates of longitudinal changes in state-level depression. Lastly, future research should test the hypothesis that higher cumulative uplifts increase positive attentional bias using subjects with varying RDS scores and changes in life events longitudinally.
References


Trivedi, M. H. (2004). The link between depression and physical symptoms. Primary care companion to the Journal of clinical psychiatry, 6(suppl 1), 12.


## Appendix

### 6.1 Discretized Criteria of Life Events

*Table 11. Indicates the binarizing criteria for life events, using 1 for the presence of a hassle or uplift and 0 otherwise.*

<table>
<thead>
<tr>
<th>Variable Name</th>
<th>UKB Code</th>
<th>1</th>
<th>0</th>
<th>NaN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hassles (Physical Health Variables + General Life Events)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall health rating general</td>
<td>2178</td>
<td>4 - poor</td>
<td>1 – excellent, 2- good, 3- fair</td>
<td>-1 – don’t know, -3 – prefer not to answer</td>
</tr>
<tr>
<td>Presence of long-standing illness, disability, or infirmity</td>
<td>2188</td>
<td>1 - Yes</td>
<td>0 - No</td>
<td>''</td>
</tr>
<tr>
<td>Wear glasses or contact lenses</td>
<td>2207</td>
<td>1 - Yes</td>
<td>0 - No</td>
<td>''</td>
</tr>
<tr>
<td>Eye problems/disorders</td>
<td>6148</td>
<td>1- Diabetes related eye disease, 2- Glaucoma, 3- Injury/trauma resulting in loss of vision, 4- Cataract, 5- Macular Degeneration, 6- Other specific eye conditions state</td>
<td>7 – None of the above</td>
<td>''</td>
</tr>
<tr>
<td>Hearing difficulty problems</td>
<td>2247</td>
<td>1 - Yes</td>
<td>0 - No</td>
<td>''</td>
</tr>
<tr>
<td>Hearing difficulty/problems with background noise</td>
<td>2257</td>
<td>1 - Yes</td>
<td>0 - No</td>
<td>''</td>
</tr>
<tr>
<td>Falls in the last year</td>
<td>2296</td>
<td>2- only one fall, 3- more than 1 fall</td>
<td>1 – No falls</td>
<td>''</td>
</tr>
<tr>
<td>Wheeze or whistling in the chest in last year breathing</td>
<td>2316</td>
<td>1-Pain/discomfort experienced</td>
<td>0:No pain/discomfort</td>
<td>''</td>
</tr>
<tr>
<td>Chest pain or discomfort</td>
<td>2335</td>
<td>1-Pain/discomfort experienced</td>
<td>0: No pain/discomfort</td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>------</td>
<td>------------------------------</td>
<td>------------------------</td>
<td></td>
</tr>
<tr>
<td>Hair/balding pattern</td>
<td>2395</td>
<td>2-4: Balding experienced</td>
<td>1- None</td>
<td></td>
</tr>
<tr>
<td>Had major operation</td>
<td>2415</td>
<td>1-Yes, had a major operation</td>
<td>0: No major operation</td>
<td></td>
</tr>
<tr>
<td>Had other major operation</td>
<td>2463</td>
<td>1- Fractured/broken bones</td>
<td>0: No fractured/broken bones</td>
<td></td>
</tr>
<tr>
<td>Had menopause</td>
<td>2724</td>
<td>1-3: Possibly to yes</td>
<td>0: No</td>
<td></td>
</tr>
<tr>
<td>Own of rent accommodation lived in</td>
<td>680</td>
<td>2- own with mortgage, 3- rent, 4- rent, 5- part rent &amp; mortgage</td>
<td>1- owned, 6- free</td>
<td></td>
</tr>
<tr>
<td>Average total household income before tax</td>
<td>738</td>
<td>1- &lt;18k, 2- 18-30k</td>
<td>3,4,5 31-100k+</td>
<td></td>
</tr>
<tr>
<td>Length of working week for main job</td>
<td>767</td>
<td>&gt; 50 hours</td>
<td>&lt;50 hours</td>
<td></td>
</tr>
<tr>
<td>Frequency of travelling from home to job workplace</td>
<td>777</td>
<td>&gt; 50 hours</td>
<td>&lt;50 hours</td>
<td></td>
</tr>
<tr>
<td>Distance between home and job workplace</td>
<td>796</td>
<td>&gt; 5</td>
<td>&lt;= 5</td>
<td></td>
</tr>
<tr>
<td>Job involves mainly walking or standing</td>
<td>806</td>
<td>3- usually, 4- always</td>
<td>1-never/rarely, 2- sometimes</td>
<td></td>
</tr>
<tr>
<td>Job involves heavy manual or physical work</td>
<td>816</td>
<td>3- usually, 4- always</td>
<td>1-never/rarely, 2- sometimes</td>
<td></td>
</tr>
<tr>
<td>Job involves shift work</td>
<td>826</td>
<td>3- usually, 4- always</td>
<td>1-never/rarely, 2- sometimes</td>
<td></td>
</tr>
<tr>
<td>Time spent driving (in hours, in day)</td>
<td>1090</td>
<td>&gt; 2</td>
<td>&lt; 2</td>
<td></td>
</tr>
<tr>
<td>Smoking/smokers in household smoking</td>
<td>1259</td>
<td>1 - yes, 2- yes 1+</td>
<td>0 – no</td>
<td></td>
</tr>
<tr>
<td>Illnesses of father</td>
<td>20107</td>
<td>1-13 - Conditions</td>
<td>-17 No condition</td>
<td></td>
</tr>
<tr>
<td>Illnesses of mother</td>
<td>20110</td>
<td>1-13 - Conditions</td>
<td>-17 No condition</td>
<td></td>
</tr>
<tr>
<td>Variable Name</td>
<td>UKB Code</td>
<td>0</td>
<td>1</td>
<td>NaN</td>
</tr>
<tr>
<td>---------------------------------------------------</td>
<td>----------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Alcohol intake frequency</td>
<td>1558</td>
<td>1: daily</td>
<td>2-6:3-4 times to never</td>
<td></td>
</tr>
<tr>
<td>Other eyesight problems</td>
<td>2227</td>
<td>1 - Yes</td>
<td>0 - No</td>
<td></td>
</tr>
<tr>
<td>Attendance/ disability/mobility allowance</td>
<td>6146</td>
<td>Badge/allowance</td>
<td>No allowance/badge</td>
<td></td>
</tr>
<tr>
<td>Mouth/teeth dental problems</td>
<td>6149</td>
<td>Mouth/dental issues</td>
<td>No mouth/dental issues</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td>20116</td>
<td>2 - current</td>
<td>0 - Never, 1-previous</td>
<td></td>
</tr>
<tr>
<td>Pain types experienced in last month</td>
<td>6159</td>
<td>Pain experienced</td>
<td>No pain</td>
<td></td>
</tr>
</tbody>
</table>

**Uplifts (Activity + Social)**

<table>
<thead>
<tr>
<th>Variable Name</th>
<th>UKB Code</th>
<th>0</th>
<th>1</th>
<th>NaN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of days walked 10+ minutes</td>
<td>864</td>
<td>0,1,2,3</td>
<td>4,5,6,7</td>
<td></td>
</tr>
<tr>
<td>How many minutes did you spend walking on a typical day</td>
<td>874</td>
<td>&lt;1.5hr</td>
<td>&gt;1/5hr</td>
<td></td>
</tr>
<tr>
<td>Number of days doing 10+ minutes of moderate physical activities</td>
<td>884</td>
<td>0-3 days</td>
<td>4-7 days</td>
<td></td>
</tr>
<tr>
<td>Number of days doing 10+ minutes more of vigorous physical activity</td>
<td>904</td>
<td>0-3 days</td>
<td>4-7 days</td>
<td></td>
</tr>
<tr>
<td>How many times in the last 4 weeks did you go walking for pleasure?</td>
<td>971</td>
<td>1-3: Once a week or less in the last month</td>
<td>4-6: More than once a week in the last month</td>
<td></td>
</tr>
<tr>
<td>How long do you spend walking for pleasure</td>
<td>981</td>
<td>1-3: Walking for less than an hour</td>
<td>4-6: Walking for more than an hour</td>
<td></td>
</tr>
<tr>
<td>Frequency of strenuous sport in the last month</td>
<td>991</td>
<td>1-3: Frequency of strenuous activity less than once a week over the last month</td>
<td>4-6: Frequency of strenuous activity more than once a week over the last month</td>
<td></td>
</tr>
<tr>
<td>Frequency of light DIY in the last 4 weeks</td>
<td>1011</td>
<td>1-3: Frequency of light DIY less than once a week over the last month</td>
<td>4-6: Frequency of light DIY more than once a week over the last month</td>
<td></td>
</tr>
<tr>
<td>Frequency of friend/family visits social support</td>
<td>1031</td>
<td>4-7: less than once a week to never</td>
<td>1-3: more than once a week to almost daily</td>
<td>&quot;</td>
</tr>
<tr>
<td>Time spent outdoors in summer (in hours, in a day)</td>
<td>1050</td>
<td>&lt; 1 hour</td>
<td>&gt; 1 hour</td>
<td>&quot;</td>
</tr>
<tr>
<td>Time spent outdoors in winter (in hours, in a day)</td>
<td>1060</td>
<td>&lt; 1 hour</td>
<td>&gt; 1 hour</td>
<td>&quot;</td>
</tr>
<tr>
<td>Ability to confide</td>
<td>2110</td>
<td>Once a month or less</td>
<td>Once a week or more</td>
<td>&quot;</td>
</tr>
<tr>
<td>Frequency of heavy DIY in last 4 weeks</td>
<td>2624</td>
<td>Less than once a week</td>
<td>Once a week or more</td>
<td>&quot;</td>
</tr>
<tr>
<td>Transport type for commuting to job workplace</td>
<td>6143</td>
<td>Indoor transport</td>
<td>Outdoor transport</td>
<td>&quot;</td>
</tr>
<tr>
<td>Types of physical activity in last 4 week</td>
<td>6164</td>
<td>No activities</td>
<td>Activities</td>
<td>&quot;</td>
</tr>
</tbody>
</table>
### 6.2 Discretized Criteria of Traumatic Events

Table 12. Indicates the full list of traumatic events, with rows shaded in grey indicating variables that were excluded from the final set of traumatic events included in the analyses. The binarizing criteria for traumatic using 1 for the presence of a trauma and 0 otherwise.

<table>
<thead>
<tr>
<th>Traumatic Event (Online Follow-Up)</th>
<th>Code as NaN</th>
<th>1: Trauma</th>
<th>0: Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Felt loved as a child</td>
<td>Prefer not to answer (-818)</td>
<td>Often (3) Very often true (4) Sometimes true (2)</td>
<td>Never true (0) rarely true (1)</td>
</tr>
<tr>
<td>2 Physically abused by family as a child</td>
<td>Prefer not to answer (-818)</td>
<td>Often (3) Very often true (4) Sometimes true (2)</td>
<td>Never true (0) rarely true (1)</td>
</tr>
<tr>
<td>3 Felt hated by family member as a child</td>
<td>Prefer not to answer (-818)</td>
<td>Often (3) Very often true (4) Sometimes true (2)</td>
<td>Never true (0) rarely true (1)</td>
</tr>
<tr>
<td>4 Sexually molested as a child</td>
<td>Prefer not to answer (-818)</td>
<td>Often (3) Very often true (4) Sometimes true (2)</td>
<td>Never true (0) rarely true (1)</td>
</tr>
<tr>
<td>5 Someone to take to doctor when needed as a child</td>
<td>Prefer not to answer (-818)</td>
<td>Often (3) Very often true (4) Sometimes true (2)</td>
<td>Never true (0) rarely true (1)</td>
</tr>
<tr>
<td>6 Been in a confiding relationship as an adult</td>
<td>Prefer not to answer (-818)</td>
<td>Often (3) Very often true (4) Sometimes true (2)</td>
<td>Never true (0) rarely true (1)</td>
</tr>
<tr>
<td>7 Physical violence by partner or ex-partner as an adult</td>
<td>Prefer not to answer (-818)</td>
<td>Often (3) Very often true (4) Sometimes true (2)</td>
<td>Never true (0) rarely true (1)</td>
</tr>
<tr>
<td>8 Belittlement by partner or ex-partner as an adult</td>
<td>Prefer not to answer (-818)</td>
<td>Often (3) Very often true (4) Sometimes true (2)</td>
<td>Never true (0) rarely true (1)</td>
</tr>
<tr>
<td>9 Sexual interference by partner or ex-partner without consent as an adult</td>
<td>Prefer not to answer (-818)</td>
<td>Often (3) Very often true (4) Sometimes true (2)</td>
<td>Never true (0) rarely true (1)</td>
</tr>
<tr>
<td>10 Able to pay rent/mortgage as an adult</td>
<td>Prefer not to answer (-818)</td>
<td>Often (3) Very often true (4) Sometimes true (2)</td>
<td>Never true (0) rarely true (1)</td>
</tr>
<tr>
<td></td>
<td>Description</td>
<td>Prefer not to answer (-818)</td>
<td>Yes, but not in the last 12 months</td>
</tr>
<tr>
<td>---</td>
<td>-----------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>11</td>
<td>20531- Victim of sexual assault</td>
<td>Prefer not to answer (-818)</td>
<td>Yes, but not in the last 12 months</td>
</tr>
<tr>
<td>12</td>
<td>20529- Victim of physically violent crime</td>
<td>Prefer not to answer (-818)</td>
<td>Yes, but not in the last 12 months</td>
</tr>
<tr>
<td>13</td>
<td>20526- Been in serious accident believed to be life-threatening</td>
<td>Prefer not to answer (-818)</td>
<td>Yes, but not in the last 12 months</td>
</tr>
<tr>
<td>14</td>
<td>20530- Witnessed sudden violent death</td>
<td>Prefer not to answer (-818)</td>
<td>Yes, but not in the last 12 months</td>
</tr>
<tr>
<td>15</td>
<td>20528- Diagnosed with life-threatening illness</td>
<td>Prefer not to answer (-818)</td>
<td>Yes, but not in the last 12 months</td>
</tr>
<tr>
<td>16</td>
<td>20527- Been involved in combat or exposed to war-zone</td>
<td>Prefer not to answer (-818)</td>
<td>Yes, but not in the last 12 months</td>
</tr>
<tr>
<td>17</td>
<td>20497- Repeated disturbing thoughts of stressful experience in past month</td>
<td>Prefer not to answer (-818)</td>
<td>A little bit (1)</td>
</tr>
<tr>
<td>18</td>
<td>20498- Felt very upset when reminded of stressful experience in past month</td>
<td>Prefer not to answer (-818)</td>
<td>A little bit (1)</td>
</tr>
<tr>
<td>19</td>
<td>20495- Avoided activities or situations because of previous stressful experience in past month</td>
<td>Prefer not to answer (-818)</td>
<td>A little bit (1)</td>
</tr>
<tr>
<td>20</td>
<td>20496- Felt distant from other people in past month</td>
<td>Prefer not to answer (-818)</td>
<td>A little bit (1)</td>
</tr>
<tr>
<td>21</td>
<td>20494- Felt irritable or had angry outbursts in past month</td>
<td>Prefer not to answer (-818)</td>
<td>A little bit (1)</td>
</tr>
</tbody>
</table>
### 6.3 Discretized Criteria of Traumatic Events

*Table 13. Indicates Bonferroni corrected (<0.05) P value, T value and R2 value for independent hassles and uplifts analyses with and without trauma (to 2 d.p or 1 s.f.). The shaded rows indicate significant life events (<0.05).*

<table>
<thead>
<tr>
<th>Hassles</th>
<th>Regression Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without Trauma</td>
</tr>
<tr>
<td></td>
<td>P Value</td>
</tr>
<tr>
<td>Accommodation Lived in</td>
<td>0.07</td>
</tr>
<tr>
<td>Average Household Income</td>
<td>0.08</td>
</tr>
<tr>
<td>Travelling Frequency to Workplace</td>
<td>0.05</td>
</tr>
<tr>
<td>Overall General Health Rating</td>
<td>0.03</td>
</tr>
<tr>
<td>Longstanding Illness Disability Infirmity Presence</td>
<td>0.04</td>
</tr>
<tr>
<td>Hearing Difficulty Problems with Background Noise</td>
<td>0.01</td>
</tr>
<tr>
<td>Falls In the Last Year</td>
<td>0.07</td>
</tr>
<tr>
<td>Chest Pain or Discomfort</td>
<td>0.08</td>
</tr>
<tr>
<td>Attendance Disability Mobility Allowance</td>
<td>0.09</td>
</tr>
<tr>
<td>Mouth/Dental Problems</td>
<td>0.07</td>
</tr>
<tr>
<td>Pain Type Experienced in Last Month</td>
<td>Uplifts</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Mins Spent Walking in A Day</td>
<td>0.07</td>
</tr>
<tr>
<td>No Of Days of Vigorous Physical Activity Ten Plus Mins</td>
<td>0.11</td>
</tr>
<tr>
<td>Time Spent Walking for Pleasure</td>
<td>0.08</td>
</tr>
<tr>
<td>Frequency Of Visits Friends Family</td>
<td>0.04</td>
</tr>
<tr>
<td>Time Spent Outdoors in Winter</td>
<td>0.07</td>
</tr>
<tr>
<td>Ability To Confide</td>
<td>0.02</td>
</tr>
<tr>
<td>Frequency Of Heavy DIY in Last Month</td>
<td>0.07</td>
</tr>
<tr>
<td>Type Of Physical Activity in Last Month</td>
<td>0.09</td>
</tr>
</tbody>
</table>
6.4 PROFUMO Modes

Figure 19. Below are the group maps of all 20 modes, from which modes 10, 13, and 14 were excluded from analyses in Chapters 3 and 4. Color bar scale: red indicates positive elements of the network and green indicates negative elements of the network.