Master's Thesis of Psychology

Distinct roles of depressive symptoms and their neural correlates in the prediction of cognitive function in older adults

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Abstract

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In the rapidly aging world, late-life depression (LLD) is a highly debilitating condition in that even subclinical symptoms can negatively impact cognitive functioning in older adults. However, the heterogeneity of the neural underpinnings of depressive symptoms in cognitive decline in the nonclinical population is not well understood. Thus, this study aimed to investigate the role of the underlying neural mechanisms of affective, motivational, and somatic symptoms of depression in predicting performance in episodic memory, processing speed, and executive function in healthy older adults. One hundred fifty-seven healthy older adults (mean age = 72.78, SD = 6.53, 60.5% female) were administered the Korean Geriatric Depression Scale (GDS), neuropsychological assessment, and resting-state fMRI. Items from the GDS were divided into seven symptom subgroups, which were then categorized into three symptom clusters (i.e., affective, motivational, and somatic) according to previous studies. Episodic memory, semantic memory, processing speed, and executive function were measured by the Elderly Memory disorder Scale, the Vocabulary subtest from the K-WAIS-IV, the Trail Making Test A, the Stroop test, and Controlled Oral Word Association Test. Linear regression models were

generated with symptom subgroup scores as independent variables and neuropsychological scores as dependent variables, controlling for age, sex, and years of education. For each individual, seven resting-state functional connectivity matrices (FC matrices) showing the association of each symptom subgroup score were constructed. Each of these FC matrices then underwent connectivity-based predictive modeling (CPM), where leave-one-out-cross-validation and random permutation were utilized to produce and test the predictive power of models explaining the relationship between the neural correlates of symptom subgroups and neuropsychological scores. For models that were statistically significant, functional connections that contributed most to model construction were identified. Although there were no significant relationships between behavioral data of depressive symptoms and cognitive performance, neural correlates for affective symptoms predicted episodic and semantic memory, and neural correlates for somatic symptoms predicted semantic memory, processing speed, and executive function. Thus, the current study found evidence for the neural underpinnings of differential relationships between the three depressive symptom clusters and cognitive functions. Additionally, the results suggest that subclinical depressive symptoms can affect the trajectory of cognitive aging in older adults with subclinical depression.

Keywords: late-life depression, neuropsychological function, depressive symptoms, resting-state functional connectivity, connectivity-based predictive modeling
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Chapter 1. Introduction

In the rapidly aging contemporary world, securing the quality of the later years of life has become an important priority. However, in doing so, late-life depression (LLD) is a multifaceted hinderance. LLD refers to the occurrence of major depressive disorder in adults 60 years of age or older, including both early and late onsets (Butters et al., 2008). Worldwide, 1-4% of older adults are clinically diagnosed of this condition, and 8-16% are reported to suffer from clinically significant syndromes without diagnosis (Blazer, 2003). In South Korea, the prevalence of LLD diagnosed by the DSM-IV is estimated to be as high as 5.37% (Park et al., 2010), and the estimate escalates to 17.8% when considering individuals who experience significant symptoms without clinical diagnosis (Park et al., 2012). LLD not only poses a threat to the quality of life of older adults, (Doraiswamy et al., 2002), but is also known to negatively influence cognitive functioning (Butters et al., 2000; Butters et al., 2008), which is similar to the younger depressed population (Park, 2019). Further, LLD is well known to be a risk factor for mild cognitive impairment or dementia (Andersen et al., 2005; Chen et al., 2008; Jorm, 2000; Saczynski et al., 2010). The cognitive difficulties that follow LLD are associated with worse treatment response as well (Pimontel et al., 2012). Therefore, understanding the underlying mechanism of depressive symptoms impacting cognition is imperative to promote well-being in older adults.

1.1. Cognitive impairment in late life depression

Three facets of cognitive functioning are often mentioned as receiving negative

influence from depressive symptoms: processing speed, executive function, and episodic memory (Naismith et al., 2012). Although these functions are known to naturally deteriorate as an individual ages (Salthouse, 2010), studies show that symptoms of depression can exert negative influence on the above three domains of cognition orthogonal to the effect of aging. Processing speed is suggested to be an underpinning mechanism accounting for impairments in other domains of cognitive function in LLD (Butters et al., 2008; Sexton et al., 2012; Sheline et al., 2006), and has been reported to be associated with poor treatment response (Naismith et al., 2012). Executive function is another cognitive domain reported to play a "core" role in the wide range of cognitive deficits in many studies (Sheline et al., 2006), and also is known to be associated with poor clinical outcome and prognosis (Baldwin et al., 2004; Sneed et al., 2007). Deficits in episodic memory may not be as severe as other domains of cognitive functions in LLD, and the literature on memory dysfunction in LLD present heterogeneous results (Herrmann et al., 2007; Köhler et al., 2010; Naismith et al., 2003). This may be due to the diverse factors that can influence memory capacity, such as cerebrovascular disease or neurodegenerative changes that influence the hippocampus. It may also be the fact that memory consists of three subfunctions (i.e., encoding, storing, and retrieval) that leads studies using different measures for probing memory to bear differential results. Nevertheless, episodic memory in LLD is reported to be predictive of the functional disability in patients (Naismith et al., 2012).

Other than the three main cognitive domains mentioned above, semantic memory is another aspect of memory that can be influenced by symptoms of depression, especially in older adults suffering clinical levels of cognitive decline. Lehrner et al. (2017) reports that semantic memory measured by a capital-to-country

matching task and vocabulary task was impaired in patients with subjective cognitive decline, mild cognitive impairment, and Alzheimer's disease, with a significant association with depressive symptoms. However, many studies suggest that depressive symptoms alone do not account for impairment in semantic memory (Brunet et al., 2011; Callahan et al., 2014; Elderkin-Thompson et al., 2004). In contrast, one study involving a wide spectrum of elderly patients reports that patients with affective disorders displayed mild impairment in semantic memory (Vogel et al., 2014)

Individuals with subclinical symptoms of LLD may suffer impaired cognitive functions as well. Older adults with depressive symptoms in the absence of a clinical diagnosis of major depressive disorder are reported to show consequences in episodic memory (Latorre et al., 2013), increased cognitive impairment at baseline (Elderkin-Thompson et al., 2007) and at 1-year follow-up compared to nondepressed counterparts (Han et al., 2008), and an elevated risk of dementia (Boyle et al., 2010). To date, there are no studies that have observed the effect of depressive symptoms on semantic memory in healthy older adults without cognitive impairment. Nevertheless, understanding the relationship between cognitive impairment and depressive symptoms in the healthy population is crucial for securing the health of the subclinical population as well as the clinical population.

1.2. Heterogeneous impact of depressive symptoms on cognition

Heterogeneity of depressive symptoms. Depression is a condition encompassing a wide variety of symptoms. The DSM-5 proposes nine different

symptoms (American Psycholoical Association, 2013), and a study utilizing more recent methodology suggests that there may exist up to 28 “non-DSM” symptoms of depression (Fried et al., 2016). This heterogeneity is reported to persist throughout the life cycle, becoming the most prominent in later life (Blazer, 2003)

Factor analyses of scales designed to probe symptoms of depression spawn distinct symptom clusters as well. The Center for Epidemiologic Studies – Depression (CES-D) Scale (Radloff, 1977), a 20-item instrument designed for the nonclinical population, consists of a well-replicated four-factor structure: depressive affect, positive affect, somatic complaints, and interpersonal problems (Devins et al., 1988). The Inventory of Depressive Symptomatology (Rush et al., 1996), a 30-item self-report instrument, can be divided into three factors: cognitive/mood, anxiety/arousal, and vegetative in the general adult population (Rush et al., 1996), and mood, motivational, and somatic in the elderly population (Hegeman, Wardenaar, et al., 2012). Korszun et al. (2004) applied exploratory factor analysis to group 24 depression-related items from the Schedules for Clinical Assessment in Neuropsychiatry (Aboraya et al., 1998) into four distinct symptom dimensions: mood symptoms, anxiety, psychomotor agitation, and appetite gain and hypersomnia. According to the studies mentioned above, depressive symptoms seem to generally group into three broad clusters: affective, motivational, and somatic. Affective symptoms include negative mood or the lack of positive mood. Motivational symptoms include fatigue, agitation, and the lack of interest in a variety of activities. Somatic symptoms include change in appetite or sleeping pattern, and subjective cognitive decline.

Heterogeneity of the effect of depressive symptoms on cognitive function. A review by Fried and Nesse (2015) suggests that the heterogeneity of depressive

symptoms results in different biological correlates, response to antidepressants, risk factors, and functional impairment. In particular, the differential impact on distinct symptoms on different facets of cognition is reflected in the conflicting results of studies on the impact of overall depressive symptoms on cognitive functioning (Rashidi-Ranjbar et al., 2020). In one study, elderly participants with depression displayed impaired executive function, while having relatively intact verbal and visuospatial memory (Dybedal et al., 2013). However, in another study, elderly participants with depression had impaired attention and memory despite preserved processing speed and executive function (Yue et al., 2015). In yet another study by Alexopoulos et al. (2012) there was no significant difference in the cognitive profiles between depressed versus healthy elderly adults.

Korten et al. (2014) suggest that this discrepancy may possibly be due to the heterogeneous impacts of depressive symptom clusters on different cognitive domains. In their study of 510 depressed and healthy elderly adults, three subscales of the CES-D each showed distinct profiles of cognitive impairment. Symptoms related to mood predicted worse working memory and processing speed; symptoms related to motivation predicted worse episodic memory and processing speed; and symptoms related to somatic conditions predicted worse working memory. Two other studies each on patients with clinical dementia and depression showed yet another type of clinical profile where only symptoms related to motivation were related to verbal fluency (Janzing et al., 2005) and executive function and processing speed (Feil et al., 2003).

Similarly designed studies on community-dwelling older adults bear results that suggest that the relationship between depressive symptoms and cognitive decline is not uniform. A large-scale study involving 22,777 healthy older participants (Castro-

Costa et al., 2007) showed that motivational symptoms negatively influenced verbal fluency, while affective symptoms did not show any significant relationship with cognitive functioning. However, in another study, affective symptoms negatively influenced executive functions (i.e., attention, motor functioning, and verbal fluency) while somatic symptoms additionally impacted memory (Baune et al., 2007). Other studies utilizing the same scale for depression (i.e., the CES-D), however, reported that memory was not affected by any of the symptom clusters (Brailean et al., 2016; Dotson et al., 2014). In these studies, affective symptoms influenced executive functions, and somatic symptoms were related to both executive functions and processing speed. Another study applying a four-factor subscale design for the GDS (Hall & Davis, 2009; Hall et al., 2011) found that symptoms related to subjective cognitive decline predicted executive functions and episodic memory, whereas apathy predicted a processing speed. Finally, a study on African American older adults strongly implies a relationship between affective symptoms and memory function (Turner et al., 2015). Details of the above studies can be found in Table 1.

1.3. Resting-state functional connectivity

Spontaneous brain activity while the individual is at resting state is known to reflect the neuronal baseline activity of the brain, which occurs consistently across time (Damoiseaux, 2006). Accordingly, the connectivity between brain regions during this activity is used to analyze the intrinsic functional construction of the brain, which is interpreted as the representation of the individual's inherent state (Biswal et al., 1995; Fox & Raichle, 2007). This type of modality for neuroimaging is referred

Table 1. A review of studies on the relationship between LLD symptom clusters and cognitive function domains

Study	Population (sample size)	Depression scale	Symptom cluster	Cognitive domain
Castro-Costa et al. (2007)	community (n = 22777)	Euro-D	motivational	verbal fluency
Baune et al. (2007)	community (n = 365)	CES-D	depressed affect	attention, motor function
			somatic	attention, motor function, memory
			disturbed positive affect	verbal fluency
Hall et al. (2011)	community (n = 356)	GDS	cognitive impairment	executive function, episodic memory
			apathy	processing speed
Dotson et al. (2014)	community* (n = 71)	CES-D	depressed affect	executive function
			somatic	working memory
Turner et al. (2015)	community (n = 298)	CES-D	lack of positive affect	global cognition, episodic memory, perceptual speed
		GDS	anhedonia	semantic memory
			negative affect	global cognition, episodic/semantic/working memory
Brailean et al. (2016)	community (n = 3107)	CES-D	depressed affect	inductive reasoning
			somatic	inductive reasoning, processing speed
Feil et al. (2003)	depressed (n = 89)	HAM-D	apathy	executive function, processing speed
Janzing et al. (2005)	dementia (n = 60)	DSM-III-R	motivational	verbal fluency
Korten et al. (2014)	depressed (n = 510)	IDS	motivational	episodic memory, processing speed
			mood	working memory, processing speed

* including younger adults

to as resting-state functional connectivity (rs-fc), and is used widespread in clinical studies to identify abnormal brain-behavior relationships and translate neuroimaging findings to clinical care (Fox & Greicius, 2010). This is because rs-fc provides information about the brain's default energy consummation, and the variation in this basic metabolism is deemed more informative compared to the small changes (usually less than 5%) in neuronal activity that are acquired during task fMRI (Raichle & Mintun, 2006). Also, its signal-to-noise ratio is reported to be approximately three times as higher than task fMRI. Finally, because rs-fc imaging does not require the participant to engage in a particular activity or exert attention to a task, it is more convenient to administer to a wider range of participants.

Resting-state functional connectivity in late life depression. Many previous studies imply abnormal rs-fc in the default mode, executive control, frontolimbic, and corticostriatal networks in LLD compared to healthy elderly counterparts (Rashidi-Ranjbar et al., 2020; Tadayonnejad & Ajilore, 2014), supporting the claim that LLD is better explained with a "network dysfunction model" rather than a "lesion pathology model". Kenny (2010) found that remitting LLD patients showed a wide range of brain areas with significant connectivity with the head of the caudate nucleus, while health controls mostly displayed frontal connectivity. Especially, the author suggests that increased connectivity between the caudate and medial prefrontal regions suggest that a circuit-level dysfunction related to emotional processing may induce the abnormally low mood in LLD. A study utilizing network analysis of resting-state fMRI reports connectivity to be globally increased in depressed elderly adults, along with more network hubs found in posterior medial-parietal areas. Especially, the caudate nucleus was shown to have high connectivity with the posterior cingulate cortex (PCC), a core hub of the default mode network

(DMN). These results implicate the differentiating role of brain regions associated with emotional regulation and self-referencing in depressed elderly adults (Bohr et al., 2012). Another study implementing independent component analysis (ICA) showed that depressed elderly adults had increased connectivity between the DMN and right posterior superior temporal sulcus, which is an area related to social perception (Eyre et al., 2016).

Other studies have investigated the underlying neural mechanisms in individual cognitive domains that are impaired in LLD. One study found that the internetwork rs-fc between the left CCN and insular regions of the salience network (SN) was correlated with deficits in executive functions, but no internetwork measures showed correlations with episodic memory performance (Li et al., 2017). A study utilizing regional homogeneity reported that the dorsal anterior cingulate cortex (dACC) was strongly implicated in LLD patients to healthy controls, and that the resting-state regional homogeneity in this area also predicted decline in executive functions in LLD (Respino et al., 2020). A diffuse tensor imaging (DTI) study on clinically depressed older adults found that executive function and processing speed, postulated to be the core cognitive deficits of LLD, are grounded in decreased frontal-striatal-limbic connections, especially in the uncinate fasciculus and genu of corpus callosum (Sexton et al., 2012).

Despite the abundance of research on the neural underpinnings of LLD as a single construct, there is a relative paucity in studies that tease out the neural correlates of individual symptom clusters of LLD. Alexopoulos et al. (2012) suggested a “double dissociation” of the cognitive control network (CCN) and DMN in LLD, each representing cognitive and affective dysfunctions, and later found that depressed elders showing apathy had altered functional connectivity in two seeds,

the nucleus accumbens and dACC (Alexopoulos et al., 2013). A study focused on neuroticism in LLD found that negative affect is associated with stronger rs-fc between medial prefrontal areas and the amygdala and PCC in depressed older adults to never-depressed controls (Steffens et al., 2017).

Even fewer studies probe the rs-fc mechanisms under the relationship between individual depressive symptoms and cognitive performance. One study differentiated LLD with and without mild cognitive impairment (MCI) by utilizing the resting-state functional connectivity of the amygdala, finding that cognitively intact patients with LLD showed decreased connectivity between the amygdala and frontoparietal regions and increased connectivity with posterior DMN regions, while patients with comorbid MCI displayed a dampened effect of increased connectivity with the DMN (Li et al., 2015). More specifically, in cognitively unimpaired participants, the severity of depressive and anxious symptoms was predicted by connectivity between the amygdala and left medial temporal gyrus (MTG), while in patients with comorbid MCI there was a much wider extent of functionally connected regions predicting the severity of depressive symptoms. Another more recent study on clinically depressed older adults found that rs-fc in the CCN accounted for anhedonia and fatigue in LLD, and was implicated to effect episodic memory and working memory (Gandelman et al., 2019).

Notwithstanding, to date, very few studies directly address the neural correlates under the relationship between distinct symptom clusters of LLD and profiles of cognitive impairment in healthy older adults. Because there is a growing body of evidence suggesting that subthreshold symptoms of depression have neural correlates that are similar to major depression in older adults (Naismith et al., 2012), it is important to further investigate this area in depth.

1.4. Objectives and hypotheses

As discussed above, LLD is a heterogeneous disorder with varied patterns of symptom clusters showing complex relationships with different domains of cognitive function, which affect both the clinical and healthy elderly population. However, the current literature fails to display a clear association among the distinct cognitive profiles of individual symptom clusters of LLD. Moreover, there is a stark lack of resting-state fMRI studies probing the underlying mechanism of the differential relationships between LLD symptoms and cognitive functions in the community-dwelling elderly population.

The purpose of this study is twofold. First, this study attempts to replicate previous studies on the community population that report differential cognitive profiles displayed in distinct LLD symptoms. Second, this study aims to investigate the underlying neural correlates of the differential cognitive domains associated with each symptom cluster in an explorative manner. As such, the following hypotheses are tested:

(1) Different symptoms will predict different patterns of decline in cognitive domains: 1) affective symptoms will predict decline in episodic memory, semantic memory, and executive functions; 2) motivational symptoms will predict decline in processing speed and executive functions; 3) somatic symptoms will predict decline in processing speed and executive functions.

(2) The resting-state functional connectivity related to different symptoms will predict different patterns of decline in cognitive domains: 1) neural correlates of affective symptoms will predict decline in episodic

memory, semantic memory, and executive functions; 2) neural correlates of motivational symptoms will predict decline in processing speed and executive function; 3) neural correlates of somatic symptoms will predict decline in processing speed and executive function.

Chapter 2. Methodology

2.1. Participants

The participants of this study were a subset of a larger group of the Korean Social Life, Health, and Aging Project (KSHAP). A total of 200 elderly adults were recruited from two rural towns in South Korea, and were administered demographic and sociopsychological questionnaires, neuropsychological assessment, and resting-state fMRI. The participants' years of education was quantified as the number of years actually spent at school. The participants were then screened for exclusion criteria, which are as follows: 1) a history of psychiatric disorders or neurological damage, 2) use of psychiatric drugs, 3) experience of unconsciousness lasting more than 20 minutes, 4) clinical levels of cognitive decline (CDR > 0), 5) excessive head movement in MR images (i.e., mean FD > .5mm and less than 50% of volumes remaining after scrubbing; Drysdale et al., 2017; Power et al., 2012), and 6) other artifacts that render MRI analysis impossible.

As a result, 157 healthy participants remained for data analysis. There were more women than men (96 women, 62 men), and the mean age was 72.78 years (*SD* = 6.53). All the participants provided written informed consent and were given financial compensation for their participation at the end of the session. This study was approved by the Institutional Review Board (IRB) at Seoul National University.

2.2. Measures

The Geriatric Depression Scale. The Geriatric Depression Scale (GDS;

Yesavage et al., 1982) was used to measure overall depressive symptoms of the participants. The GDS is a self-report questionnaire consisting of 30 yes-or-no questions about symptoms that appear commonly in late-life depression, and has been reported to be able to capture subclinical levels of depression (Montorio & Izal, 1996). Examples of the items are as follows: “Are you basically satisfied with your life?”; “Have you dropped many of your activities and interests?”; “Do you worry a lot about the past?”; “Do you frequently feel like crying?”; “Do you have trouble concentrating?”. This study utilized the Korean version of the GDS, translated and validated by Jung et al. (1997). According to an explorative factor analysis in this validation study, 27 of the 30 items were divided into seven subgroups: core depressive symptoms, lack of pleasure, lack of happiness, agitation, cognitive inefficiency, withdrawal, and lack of motivation. The core depressive symptoms subgroup contains six items pertaining to negative affectivity (e.g., “Do you worry a lot about the past?”, “Do you frequently feel like crying?”). The lack of pleasure subgroup contains four items about anhedonia (e.g., “Do you feel that your life is empty?”, “Do you often get bored?”). The lack of happiness subgroup also contains five items showing negative correlation with a feeling of well-being (e.g., “Do you find life very exciting?”, “Do you think it is wonderful to be alive now?”). The agitation subgroup consists of four items on mental instability (e.g., “Are you basically satisfied with your life?”, “Is it easy for you to make decisions?”). The cognitive inefficiency subgroup consists of four items on the subjective difficulty of cognitive functioning (e.g., “Do you feel you have more problems with memory than most?”, “Is it hard for you to get started on new projects?”). The withdrawal subgroup contains two items pertaining to general social withdrawal (“Do you prefer to stay at home rather than go out and do things?”, “Do you prefer to avoid social

occasions?"). The lack of motivation subgroup contains two items on the lack of energy in general ("Do you feel full of energy?", "Do you enjoy getting up in the morning?"). In this study, the same subgroups were used after undergoing confirmative factor analysis to check whether the seven-factor structure has acceptable fit for the given data. The seven subgroups were then categorized into three symptom clusters according to the semantic meaning of the constituting items, based on previous studies on diverse depression scales (Adams et al., 2004; Devins et al., 1988; Hegeman, Wardenaar, et al., 2012; Korszun et al., 2004). As a result, three symptom clusters were defined: (1) affective symptoms, (2) motivational symptoms, and (3) somatic symptoms (Table 2). Analysis was conducted based on the GDS subgroups rather than the integrative symptom clusters to enable more specific interpretation of the relationship between symptoms and cognitive domains.

Table 2. Three symptom clusters of the GDS

GDS subgroup	Symptom cluster	Content
Core depressive symptoms Lack of pleasure Lack of happiness	Affective symptoms	Negative affect and lack of positive affect
Agitation Withdrawal	Motivational symptoms	Lack of motivation
Cognitive inefficiency Lack of motivation	Somatic symptoms	Lack of somatic energy, subjective cognitive decline

Neuropsychological Assessment. The following neuropsychological assessments were used to attain indices for episodic memory, processing speed, and executive function (Table 3).

Episodic memory was measured by the Elderly Memory disorder Scale (EMS; Chey, 2006). The EMS is a tool for assessing both verbal and visuospatial learning and memory in older adults with less exposure to education. It is thus adequate for investigating the cognitive performance of the Korean elderly population, who

Table 3. Neuropsychological measures

Function	Measures	Indices
Episodic memory	Elderly Memory disorder Scale	Recall index, Recognition index
Semantic memory	K-WAIS-IV Vocabulary	Accuracy of definition
Processing speed	Train Making Test A	Time to completion
Executive Function		
Cognitive control	K-CWST	Interference Score
Fluency	COWAT (animal, store)	Number of items produced
Working memory	Elderly Memory disorder Scale	Working memory index

K-CWST: Korean Color Word Stroop Test; COWAT: Controlled Oral Word Association Test

generally have had fewer years of education than their western counterparts. Two indices calculated from three tasks were used as indices of episodic memory. The three tasks used were the Elderly Verbal Learning Test (EVLT), Simple Rey Figure Test (SRFT), and Story Recall Test (SRT).

The EVLT is a word list learning task based on the California Verbal Learning Test (Delis et al., 1987), measuring verbal learning and memory. A list of nine words from three distinct categories are presented to the participants over five trials. On each trial, the participant is immediately asked to repeat the items that he or she had heard in order to facilitate learning. Then after a delay of 20 to 30 minutes, the participant is asked to recall the items that he or she had learned (delayed recall). Finally, the participant is given a list of random words including the nine words presented during the learning trial, and is asked whether he or she remembers learning the word (delayed recognition).

The SRFT is a simplified version of the Rey-Osterrieth Complex Figure Task (RCFT; Rey, 1941; Osterrieth, 1944), wherein visuospatial construction and spatial learning can be measured. The participant is first asked to copy a sample figure composed of simple geometric features on a blank piece of paper. Then, the sample

and copy are taken away from view, and the participant is asked to draw what he or she had just seen and copied on another blank piece of paper. After a delay of 20 to 30 minutes, the participant is asked to draw the figure that he or she had learned on a blank piece of paper (delayed recall), and is then shown a series of figures and is asked whether the figure was included in the original figure that he or she had learned (delayed recognition).

The SRT is a task based on the Logical Memory task of the Wechsler Memory Scales version III (Wechsler, 1997), where the participant is told a short story about a kidnap. The participant is then immediately asked to retell the story in as much detail as possible. After a delay of 20 to 30 minutes, the participant is asked again to retell the story (delayed recall). Finally, the participant is asked ten questions about the story and is instructed to choose from three multiple-choice answers (delayed recognition).

From the performance of these three tasks, the long-term memory recall index (i.e., recall index) and long-term memory recognition index (i.e., recognition index) are computed. The recall index equals of the sum of the average performance in the delayed recall tasks of the EVLT, SRFT, and SRT. The recognition index equals the sum of the average performance in the delayed recognition tasks of the EVLT, SRFT, and SRT.

The Vocabulary subtask in K-WAIS-IV (Hwang et al., 2012) measures a variety of cognitive abilities, including semantic knowledge, long-term memory, and conceptualization. In this study, the Vocabulary subtask was used as an index of semantic memory. In the task, the participant is asked to define the meaning of words, and is scored by the accuracy of the definition provided. Definitions that lack abstract explanation or are overgeneralized are judged as inaccurate, and thus given a partial

score. Definitions that are completely inappropriate do not receive a score.

Processing speed was measured by part A of the modified Trail Making Test (TMT A; Park & Chey, 2003). In the task, the participant is asked to trace with a pencil encircled numbers from one to fifteen, placed randomly on a sheet of paper. It is known to measure visuospatial and motor processing speed. This study utilized the time taken to complete the task as an index of processing speed. The longer it takes for the participant to complete the task, the worse his or her processing speed is.

Executive function is a mental capacity considered as an umbrella concept, containing many different facilities (Miyake et al., 2000). Thus, this study utilized four different measures that reflect distinct facets within the wider concept of executive function.

The Korean-Color Word Stroop test (K-CWST; Kang et al., 2012) is used to measure a variety of cognitive domains, including processing speed, language processing, and cognitive control. In this study, the K-CWST was applied in order to probe cognitive control. This task consists of a word-reading trial and color-reading trial. In the word-reading trial, the word list consists of color words printed in colored ink that matches the words (e.g., “red” is printed in red ink), and the participant is asked to read the words in the list as quickly and accurately as they can. In the color-reading trial, the ink that the words are printed in are incongruent with the words (e.g., “red” is printed in blue ink), and the participant is asked to report what color the words are printed in as quickly and accurately as they can. Because the color-reading trial requires more rigorous inhibition, the interference score is calculated as the difference between the response time per item in the word-reading trial and color-reading trial is used as an index for cognitive control. The higher the interference

score, the worse the participant is at exerting cognitive control.

The Controlled Oral Word Association Test (COWAT; Kang et al., 2012) measures semantic fluency, which is a subset of verbal fluency that is relatively free of the influence of education (Ratcliff et al., 1998). In the animal trial (COWAT-a), the participant is asked to list as many animals as they can in one minute. In the store trial (COWAT-s), the participant is asked to name as many items that can be bought in a store in one minute. The total number of items produced by the participant in each trial was used as indices for semantic fluency.

The digit span test (DST) and spatial span test (SST) are well-established measures of working memory. In this study, the version of the tasks in the EMS were utilized. The DST is equivalent to the digit span test of the Wechsler Adult Intelligence Scale version IV (Wechsler, 2008). In the forward trial, the participant is presented a series of numbers, and is asked to repeat what he or she has heard in the exact order. In the backward trial, the participant is asked to repeat the string of numbers he or she has heard in the reverse order. In both trials, the examination continues until the participant is unable to give an accurate answer. The SST incorporates the Corsi block-tapping test (Kessels et al., 2000), assessing visuospatial short-term working memory. The participant is presented a 27 cm × 21 cm plastic board with ten cube blocks (3 cm × 3 cm × 3 cm) placed in an asymmetrical pattern, with the same number of cubes placed on the left and right side of the board. In the forward trial, the examiner taps the blocks in a predetermined sequence, and the participant is asked to tap the blocks in the same exact order. In the backward trial, the participant is asked to tap the blocks in the reverse order of the sequence presented by the examiner. The working memory index (WM) is computed as the sum of the maximum number of digits that the participant was able

to repeat accurately in both tasks.

fMRI acquisition and preprocessing. Functional magnetic resonance imaging (fMRI) data were acquired on a 3T Siemens MAGNETOM Trio MRI scanner with a 32-channel head coil at the Seoul National University Brain Imaging Center. T1-weighted structural images were acquired by an MPRAGE sequence (TR = 2300 ms, TE = 2.36 ms, FOV = 256 mm, 1 mm isotropic voxels). Resting-state functional images were acquired by scanning two six-minute runs of a T2*-weighted EPI sequence (TR = 2000 ms, TE = 300 ms, 30 slices, flip angle = 79°, FOV = 240 mm, 3 mm isotropic voxels). During functional imaging, participants were instructed to stay still with their eyes open, and to not fall asleep.

Image preprocessing was performed using the CONN toolbox v20b (www.nitrc.org/prjects/conn, RRID:SCR_009550) implemented with SPM12 (www.fiil.ion.ucl.ac.uk/spm/software/spm12/), running under Matlab R2020a (Mathworks). The participants' functional images were unwarped through field-map correction, and were realigned by rigid body spatial transformation using the first image as reference. Indirect segmentation and spatial normalization were performed to produce skull-stripped normalized structural images, normalized masks for gray matter, white matter, and CSF, and normalized functional volumes in MNI space. Finally, the images were smoothed with a 6 mm FWHM Gaussian kernel.

Because resting-state functional imaging data are vulnerable to head motion, the Artifact Detection Toolbox (ART; http://nitrc.org/projects/artifact_detect/) was implemented to detect outlier image frames based on motion parameters. A displacement threshold of 0.9mm and a global signal threshold of Z = 5 was used (Power et al., 2014). Participants with more than 50% of volumes existing after the elimination of the outlier scans were retained for further data analysis. The outlier

scans identified from the above procedure, along with twelve realignment parameters, were implemented as confound regressors. The confounding effects of white matter and cerebrospinal fluid signals were controlled by a noise reduction method which extracts principal components from the two sources (Behzadi et al., 2007). The data then underwent linear detrending and a temporal band-pass filter of $0.008 < f < 0.09$ Hz to discard physiological noise.

2.3. Analysis

Statistical analysis. Linear regression was used to investigate the cognitive domains that each symptom cluster predicted. GDS subgroup scores were entered as independent variables, and neuropsychological indices were inserted as dependent variables. The confounding effects of age, sex, and years of education were controlled. Statistical analysis was performed using R Studio (RStudio Team, 2020).

Resting-state functional connectivity analysis. The CONN toolbox 20b (www.nitrc.org/prjects/conn, RRID:SCR_009550) was used for rs-fc analysis. A previously defined atlas of 264 ROIs was used (Figure 1; Power et al., 2011). Among the 264 ROIs, ROIs corresponding to cerebellar areas were removed prior to analysis because full coverage of the cerebellum was not acquired from certain participants. As a result, 255 ROIs from cortical and subcortical areas were defined to be utilized in this study.

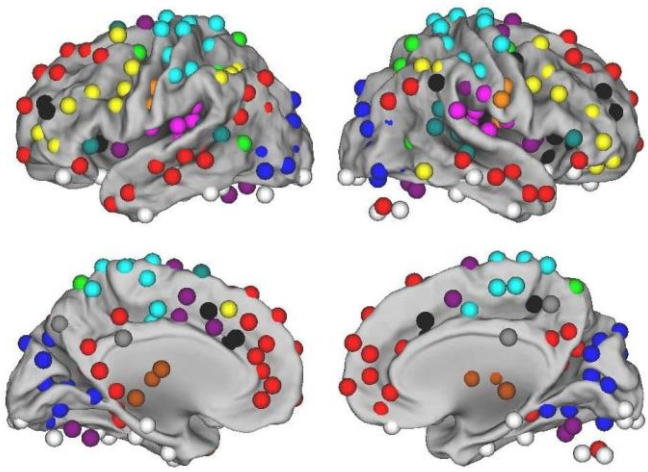

Figure 1. Parcellation for 264 cortical and subcortical regions

After controlling for the confounding effects of motion, non-gray matter signals, and physiological noise, a time series was calculated for each individual by averaging the BOLD signal of all voxels included in each ROI. Then, the Pearson correlation coefficients for each ROI's time series data were computed, and were normalized by Fisher transformation. The resulting 255×255 whole-brain correlation matrices represent each individual's resting-state connectivity profile.

To identify the neural correlates of each GDS subgroup score, nodes within the whole-brain correlation matrices that were significantly correlated with each GDS subgroup's score were extracted ($p < .001$, effects of age, sex, and years of education were controlled). Then, the corresponding nodes in each individual's whole-brain correlation matrix were extracted and reorganized into independent matrices. As a result, each participant would have seven different matrices that each represent the neural correlates of the seven subgroups of the GDS (i.e., the subgroup functional connectivity (FC) matrices).

Connectivity-based predictive modeling. Connectivity-based predictive modeling (CPM) is a data-driven method for constructing predictive models for

brain-behavior relationships utilizing connectivity data and cross-validation (Shen et al., 2017). It is a method used in order to test the ability of a functional network to predict novel participants' behavioral data, and has been used to predict neuroticism and extraversion (Hsu et al., 2018), intelligence (Finn et al., 2015), and depressive symptoms (Drysdale et al., 2017) based on rs-fc data. In this study, CPM was applied to each of the seven subgroup FC matrices and the neuropsychological performance scores.

CPM is a two-step procedure, consisting of model construction and model evaluation (Figure 2). In the model construction phase, leave-one-out cross-validation is utilized to create an optimal linear model. In other words, a linear model that can best represent the brain-behavior data after leaving one participant's data out is produced. In order to do so, the Spearman correlation between every edge of the subgroup FC matrix and neuropsychological score is calculated across each individual, producing an *r*-value and corresponding *p*-value for each edge. The edges that show significant positive or negative correlation when $p < .01$ each form a positive prediction network and negative prediction network. The sum of all the edges in the two networks are then computed to be used as summary statistics, which can be interpreted as network strength (Hsu et al., 2018). Using the two summary statistics as the independent variable and the neuropsychological score as the dependent variable, and controlling for the confounding effects of age, sex, and years of education, two linear models are produced that best fit the brain-behavior data. A general linear model (GLM) is also produced to observe the combined effects of positive and negative prediction networks. Then, the left-out participant's brain data is introduced to the models, producing predicted behavioral scores. After repeating these steps as many times as the number of participants, the correlation coefficient

between the predicted behavioral scores and actual behavioral scores is computed. This coefficient represents the model's fit for the given data.

In the model evaluation phase, the paired brain-behavior data are randomly shuffled so that the original association between the paired data is lost. Then, the randomly shuffled data is used for model-construction, producing the fit for the random model (i.e., the random fit). This process is repeated for 1000 iterations, which results in 1000 random fits. The model's predictive performance (P) is calculated as $\frac{(actual\ fit < random\ fit)}{1000}$ and is interpreted as the statistical significance of the constructed model. In other words, the ratio of random fits being better than the actual fit represents the model's performance in predicting behavioral scores with connectivity data in "novel" individuals. As with previous studies applying this method, the predictive performance of each of the models was utilized as an indicator of how strongly the neural correlates of the GDS subgroups were related to each cognitive domain measured by the neuropsychological indices (Finn et al., 2015).

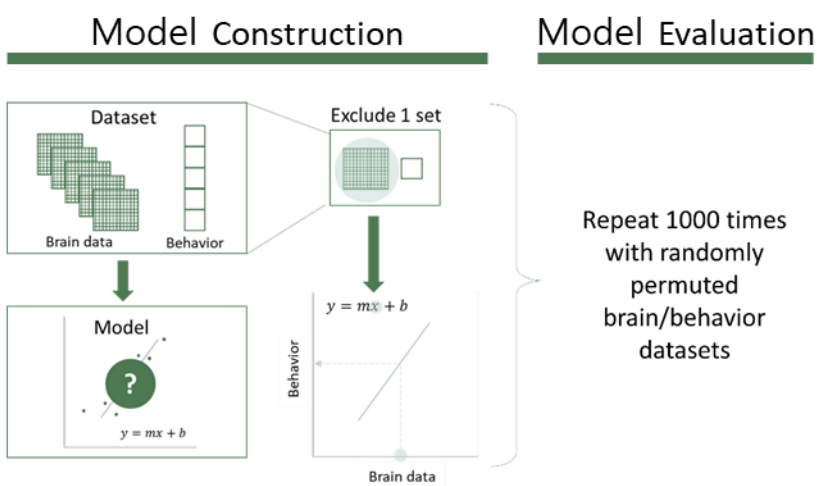

Figure 2. Connectivity-based predictive modeling

Finally, in order to observe the edges that contributed most to predicting the behavioral data, the top five edges of the GDS subgroups that were repeatedly

selected as having significant correlation with the behavioral data were selected for both the positive prediction model and negative prediction model (Finn et al., 2015; Hsu et al., 2018). These edges were interpreted as the neural correlates of the relationship between individual symptom clusters and cognitive domains (Hsu et al., 2018).

Chapter 3. Results

3.1. Demographics and behavioral measures

The participants' demographic information and behavioral measures are shown in Table 2. Ninety-six of the participants had received formal education for less than six years (61.9% of the total participants), which means that they had not gained education past the primary level in the Korean educational system. Only 12 participants reported having had higher education after graduating high school (7.7% of the total participants). The average GDS total score was 9.23, and 17 participants (10.8% of the total participants) displayed clinically moderate to severe depressive symptoms (GDS > 17, Jung et al., 1997), indicating that most of the participants did not display symptoms to the level of clinical concern.

In the neuropsychological assessments, some participants with limited literacy were not able to complete tasks that required them to read words or understand the concept of numbers. Also, some participants who completed the GDS and resting-state imaging did not participate in neuropsychological assessment altogether. These instances of null data were excluded from statistical analysis and CPM.

Table 4. Participant information

N = 157 (62 males, 39.4%)		Range	Mean (*SD*)
Demographics			
	Age	[61, 93]	72.78 (6.53)
	Years of education	[0, 23]	7.35 (4.15)
GDS scores			
	Total score	[0, 29]	9.23 (6.40)
	Subgroup scores		
	Core depressive symptoms	[0, 6]	1.643
	Lack of pleasure	[0, 4]	.8662
	Lack of happiness	[0, 5]	1.261
	Agitation	[0, 4]	.7898
	Cognitive inefficiency	[0, 4]	2.07
	Withdrawal	[0, 2]	.4395
	Lack of motivation	[0, 2]	1.019
NP scores			
	Episodic memory		
	Recall index	[.66, 2.79]	1.74 (.46)
	Recognition index	[1.78, 2.90]	2.46 (.27)
	Semantic memory		
	K-WAIS-IV vocabulary	[0, 49]	18.59 (11.45)
	Processing speed		
	TMT A time to completion	[7, 157]	31.59 (18.58)
	Executive function		
	Stroop interference score	[.02, 2.68]	.88 (.46)
	COWAT – animal items	[4, 27]	13.36 (4.14)
	COWAT – store items	[2, 34]	15.43 (6.23)
	Working memory index	[.5, 1.75]	.99 (.23)

3.2. Statistical analysis

Prior to primary analyses, confirmatory factor analysis was conducted on the GDS data of the current study based on Jung et al. (1997)'s seven-factor model. The results were within the acceptable level (Bollen, 1989) (χ^2 = 472.271, *df* = 303, CFI = .847, RMSEA = .060).

Results of linear regression analysis of the GDS subgroup scores and neuropsychological indices are shown in Table 5. Among the models generated,

agitation subgroup scores were significantly associated with TMT performance (β = .16, p = .03); cognitive inefficiency subgroup scores were significantly associated with two executive function indices (K-CWST: β = .20, p = .02; COWAT-a: β = -.18, p = .02). However, when corrected for multiple comparisons, there were no models where the association between GDS subgroup scores and neuropsychological task performance reached sufficient levels of statistical significance (i.e., $p < .005$).

3.3. Neural correlates of depressive symptoms

The resting-state functional connectivity neural correlates of the GDS subgroups were as shown in Figure 3. The top 10 edges showing the strongest correlation with GDS subgroup scores are listed in Table 6 through 12. Overall, there was a strong implication of frontolimbic areas (i.e., mPFC, thalamus, insula, and precuneus). The insula was strongly implicated for the lack of pleasure subgroup, and surprisingly, the superior frontal gyrus (SFG) repeatedly showed connections with occipital areas for the lack of happiness subgroup. Neural correlates of the agitation subgroup had nodes that are canonically known to be involved in sensory functions (i.e., insula, pre/postcentral gyri). The cognitive inefficiency subgroup displayed a predominantly negative rs-fc network compared to other symptom subgroups, and also displayed many corticostriatal connections.

Table 5. Regression results

Symptom clusters	Affective						Motivational				Somatic			
GDS subgroups	Core depressive symptoms		Lack of pleasure		Lack of happiness		Agitation		Withdrawal		Cognitive inefficiency		Lack of motivation	
Cognitive tests	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*
Episodic memory														
Recall	-.08	.29	-.05	.53	-.08	.27	-.02	.74	-.01	.92	-.06	.39	-.05	.53
Recognition	-.09	.21	-.06	.36	-.11	.09	-.11	.10	-.04	.52	-.08	.22	-.01	.87
Semantic memory														
Vocabulary	-3.32	.15	-3.15	.16	-4.70	.057	-4.80	.08	.59	.77	-.80	.71	-3.98	.10
Processing speed														
TMT A	.03	.65	-.01	.86	.04	.57	.16	.03	.08	.27	.07	.32	.07	.32
Executive function														
K-CWST	-.03	.74	-.04	.60	.03	.69	-.01	.93	-.00	.97	.20	.02	.12	.15
COWAT – a	-.12	.10	-.11	.14	-.10	.21	-.05	.53	-.03	.68	-.18	.02	-.06	.43
COWAT – s	.02	.79	.05	.52	-.01	.84	.00	.98	-.01	.94	-.03	.73	-.04	.58
WM	-.01	.85	-.00	.95	-.04	.55	-.01	.92	-.09	.23	-.06	.43	-.04	.59

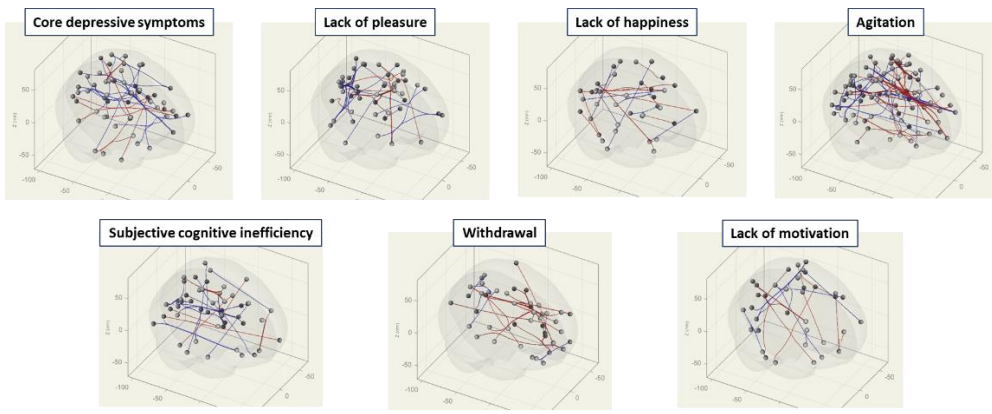

Figure 3. Resting-state connectivity networks for the seven GDS subgroups

Table 6. Top 10 edges associated with core depressive symptoms

Region of interest	MNI coordinates	Region of interest	MNI coordinates	*T* (*df* = 148)
L insula	(-35, 20, 0)	L mPFC	(-2, 38, 36)	4.55
L AG	(-44, -65, 35)	R thalamus	(9, -4, 6)	4.46
R tIFG	(53, 33, 1)	L ITG	(-68, -23, -16)	4.09
L IPL	(-39, -75, 44)	R thalamus	(9, -4, 6)	4.08
R ITG	(42, -66, -8)	L sOFC	(-21, 41, -20)	-4.03
L PostCG	(-21, -31, 61)	R MCC	(11, -39, 50)	4.01
L mPFC	(-8, 48, 23)	R MOL	(43, -72, 28)	3.95
L SPL	(-16, -46, 73)	R MFG	(32, 14, 56)	-3.92
R MOL	(29, -77, 25)	L iOFC	(-46, 31, 13)	3.91
L PostCG	(-23, -30, 72)	R MCC	(11, -39, 50)	3.90

* mPFC = medial prefrontal cortex; AG = angular gyrus; tIFG = pars triangularis of the inferior frontal gyrus; ITG = inferior temporal gyrus; sOFC = superior orbitofrontal cortex; IPL = inferior parietal lobe; PostCG = postcentral gyrus; mid MCC = middle cingulate cortex; MOL = middle occipital lobe; SPL = superior parietal lobe; MFG = middle frontal gyrus; iOFC = inferior orbitofrontal cortex

Table 7. Top 10 edges associated with lack of pleasure

Region of interest	MNI coordinates	Region of interest	MNI coordinates	*T* (*df* = 148)
L SFG	(-16, 29, 53)	R insula	(27, 16, -17)	-3.98
R PreCG	(29, -5, 54)	L MFG	(-42, 45, -2)	-3.92
L SMA	(-3, 2, 53)	L FFG	(-47, -51, -21)	3.87
L STG	(-60, -25, 14)	R insula	(27, 16, -17)	3.86
L precuneus	(-11, -56, 16)	R insula	(34, 16, -8)	-3.83
L MFG	(-32, -1, 54)	R precuneus	(11, -66, 42)	3.82
L SOL	(-27, -71, 37)	R SPL	(25, -58, 60)	-3.76
R PreCG	(42, 0, 47)	L SMG	(-54, -23, 43)	-3.76
R iOFC	(37, 32, -2)	L MFG	(-34, 55, 4)	-3.74
R PCC	(8, -48, 31)	R PreCG	(29, -5, 54)	-3.73

* SFG = superior frontal gyrus; PreCG = precentral gyrus; MFG = middle frontal gyrus; SMA = supplementary motor area; FFG = fusiform gyrus; STG = superior temporal gyrus; SMG = supramarginal gyrus; SOL = superior occipital lobe; SPL = superior parietal lobe; PreCG = precentral gyrus; iOFC = inferior orbitofrontal cortex; PCC = posterior cingulate cortex

Table 8. Top 10 edges associated with lack of happiness

Region of interest	MNI coordinates	Region of interest	MNI coordinates	*T* (*df* = 148)
L PHG	(-21, -22, -20)	L caudate	(-15, 4, 8)	-4.64
R STG	(65, -33, 20)	R SOL	(24, -87, 24)	4.38
L MOL	(-26, -90, 3)	R insula	(49, 8, -1)	3.84
L rOP	(-38, -33, 17)	R ACC	(10, 22, 27)	3.83
L PostCG	(-21, -31, 61)	L PostCG	(-53, -10, 24)	3.83
L MTG	(-44, 12, -34)	R thalamus	(9, -4, 6)	3.77
R precuneus	(6, -59, 35)	L PHG	(-21, -22, -20)	-3.73
R SFG	(13, 30, 59)	R SOL	(24, -87, 24)	3.69
R SFG	(13, 30, 59)	L MOL	(-26, -90, 3)	3.62
R SFG	(13, 30, 59)	R IOL	(43, -78, -12)	-3.59

* PHG = parahippocampal gyrus; STG = superior temporal gyrus; SOL = superior orbital lobe; MOL = middle orbital lobe; rOP = Rolandic operculum; ACC = anterior cingulate cortex; PostCG = postcentral gyrus; MTG = middle temporal gyrus; SFG = superior frontal gyrus; IOL = inferior occipital lobe

Table 9. Top 10 edges associated with agitation

Region of interest	MNI coordinates	Region of interest	MNI coordinates	*T* (*df* = 148)
L LG	(-15, -72, -8)	R insula	(37, 1, -4)	-4.86
R MTG	(46, 16, -30)	L SPL	(-28, -58, 48)	-4.46
L PostCG	(-21, -31, 61)	L PostCG	(-53, -10, 24)	4.29
L SFG	(-16, -5, 71)	L SMG	(-53, -22, 23)	4.24
L MOL	(-26, -90, 3)	R PreCG	(38, -17, 45)	4.18
R mOFC	(6, 67, -4)	R putamen	(31, -14, 2)	4.15
R PostCG	(-21, -31, 61)	L STG	(-55, -40, 14)	4.06
L SPL	(-28, -58, 48)	R PostCG	(66, -8, 25)	-4.05
R STG	(65, -33, 20)	R FFG	(27, -37, -13)	4.03
L SFG	(-20, 64, 19)	R MFG	(38, 43, 15)	-4.02

* LG = lingual gyrus; MTG = middle temporal gyrus; SPL = superior parietal lobule; PostCG = postcentral gyrus; SFG = superior frontal gyrus; SMG = supramarginal gyrus; MOL = middle occipital lobe; PreCG = precentral gyrus; mOFC = medial orbitofrontal cortex; STG = superior temporal gyrus; FFG = fusiform gyrus; MFG = middle frontal gyrus

Table 10. Top 10 edges associated with withdrawal

Region of interest	MNI coordinates	Region of interest	MNI coordinates	*T* (*df* = 148)
L SFG	(-10, 55, 39)	L MOL	(-42, -74, 0)	4.36
R rectus	(8, 48, -15)	L MTG	(-44, 12, -34)	4.13
R PreCG	(19, -8, 64)	L MFG	(-39, 51, 17)	4.06
R insula	(36, -9, 14)	R mOFC	(24, 32, -18)	-3.98
R MCC	(10, -2, 45)	L MTG	(-39, 51, 17)	3.94
R MFG	(32, 14, 56)	L ACC	(-11, 26, 25)	3.82
L STG	(-60, -25, 14)	R ACC	(10, 22, 27)	3.77
R MCC	(11, -39, 50)	R AG	(37, -65, 40)	-3.75
R SPL	(25, -58, 60)	R precuneus	(10, -46, 73)	3.66
R STG	(58, -16, 7)	L MCC	(-1, 15, 44)	3.66

* SFG = superior frontal gyrus; MOL = middle occipital lobe; MTG = middle temporal gyrus; PreCG = precentral gyrus; MFG = middle frontal gyrus; mOFC = medial orbitofrontal cortex; MCC = middle cingulate cortex; AG = angular gyrus; SPL = superior parietal lobule; STG = superior temporal gyrus

Table 11. Top 10 edges associated with cognitive inefficiency

Region of interest	MNI coordinates	Region of interest	MNI coordinates	*T* (*df* = 148)
L MOL	(-40, -88, 6)	L putamen	(-22, 7, -5)	-4.77
R MTG	(46, -59, 4)	L MCC	(-10, -2, 42)	4.75
L PHG	(-21, -22, -20)	L caudate	(-15, 4, 8)	-4.20
L thalamus	(-10, -18, 7)	L ITG	(-56, -45, -24)	-4.15
L calcarine	(-18, -68, 5)	R MOL	(29, -77, 25)	-4.04
R SMA	(13, -1, 70)	R MCC	(11, -39, 50)	3.90
L LG	(-16, -52, -1)	R ITG	(58, -53, -14)	-3.83
L MTG	(-46, 61, 21)	R SMG	(55, -45, 37)	-3.82
R MCC	(11, -39, 50)	R MCC	(10, -2, 45)	3.78
L LG	(-13, -40, 1)	L SPL	(-16, -46, 73)	-3.75

* MOL = middle occipital lobe; MTG = middle temporal gyrus; MCC = middle cingulate cortex; PHG = parahippocampal gyrus; ITG = inferior temporal gyrus; SMA = supplementary motor area; LG = lingual gyrus; SMG = supramarginal gyrus; LG = lingual gyrus; SPL = superior parietal lobule

Table 12. Top 10 edges associated with lack of motivation

Region of interest	MNI coordinates	Region of interest	MNI coordinates	*T* (*df* = 148)
L vACC	(-14, -18, 40)	R SMA	(3, -17, 58)	4.42
L MOL	(-40, -88, -6)	R PostCG	(42, -20, 55)	4.41
R rectus	(8, 48, -15)	R ACC	(2, -24, 30)	4.01
L PostCG	(-23, -30, 72)	L STG	(-55, -40, 14)	3.75
L MOL	(-26, -90, 3)	R insula	(49, 8, -1)	3.72
R STG	(65, -33, 20)	L MOL	(-40, -88, -6)	3.68
L MOL	(-40, -88, -6)	L AG	(-42, -55, 45)	3.60
R LG	(20, -66, 2)	R PreCG	(29, -17, 71)	-3.58
R FFG	(27, -59, -9)	R MTG	(46, 16, -30)	-3.55
L MOL	(-24, -91, 19)	R PostCG	(42, -20, 55)	3.53

* vACC = ventral anterior cingulate cortex; SMA = supplementary motor area; MOL = middle occipital lobe; PostCG = postcentral gyrus; STG = superior temporal gyrus; AG = angular gyrus; LG = lingual gyrus; PreCG = precentral gyrus; FFG = fusiform gyrus; MTG = middle temporal gyrus

3.4. Connectivity-based Predictive Modeling

Results of CPM between the neural correlates of each GDS subgroup and neuropsychological indices are shown in Tables 13 and 14. The model fit and significance of the model are each expressed as *r* and *P* (i.e., the predictive power of the model), where the threshold for statistical significance was set as $P < .05$ (Hsu et al., 2018). Models where the model fit was expressed as a negative correlation coefficient, or where the *p* value of the correlation coefficient did not suffice the threshold for statistical significance ($p < .05$) did not undergo permutation testing for estimating predictive power. In these cases, the *P* value is denoted as a single dash (-). Also, in cases where the number of selected edges was not sufficient enough to create a stable model, the model fit and statistical significance are expressed as Not Applicable (NaN). Many NaNs were observed for the lack of happiness subgroup and lack of motivation subgroup because the two subgroups had the least number of edges in the connectivity matrices, thus being at risk of not having enough edges to be selected as characteristic features of the predictive model.

In the affective symptom cluster, neural correlates of the lack of happiness subgroup negatively predicted recall ($r = .43$, $P = .006$). In the motivational symptom cluster, there was no statistically significant model. However, the agitation subgroup produced a marginally significant predictive model for COWAT-s ($r = .26$, $P = .083$). In the somatic symptom cluster, neural correlates of the cognitive inefficiency subgroup positively predicted TMT A ($r = .26$, $P = .043$), and the lack of motivation subgroup negatively predicted COWAT-s ($r = .32$, $P = .032$). There were no statistically significant models constructed from a GLM, so the corresponding results are not reported.

For each of the predictive models whose predictive power reached statistical significance, the top five edges that were selected as key features of model construction were identified as in Figure 4 and Table 15. Figure 4 is a conceptual display of the top five edges that had more influence than others in constructing predictive models, created with the BrainNet Viewer (http://nitrc.org/projects/bnv/) (Xia et al., 2013). Each panel represents influential edges in the following models: (a) lack of pleasure – vocabulary (b) lack of happiness – recall (c) cognitive inefficiency – TMT (d) lack of motivation – vocabulary (e) lack of motivation – COWAT store. The color and thickness of the edges represent the weight of the edges, which is determined by the frequency of the edge being selected for model construction. The larger the weight, the thicker the edges are depicted. The size of the nodes reflects the nodes' strength centrality, which is calculated as the sum of the weight of edges adjacent to each node. More information about the ROIs included in Figure 4 are detailed in Table 15.

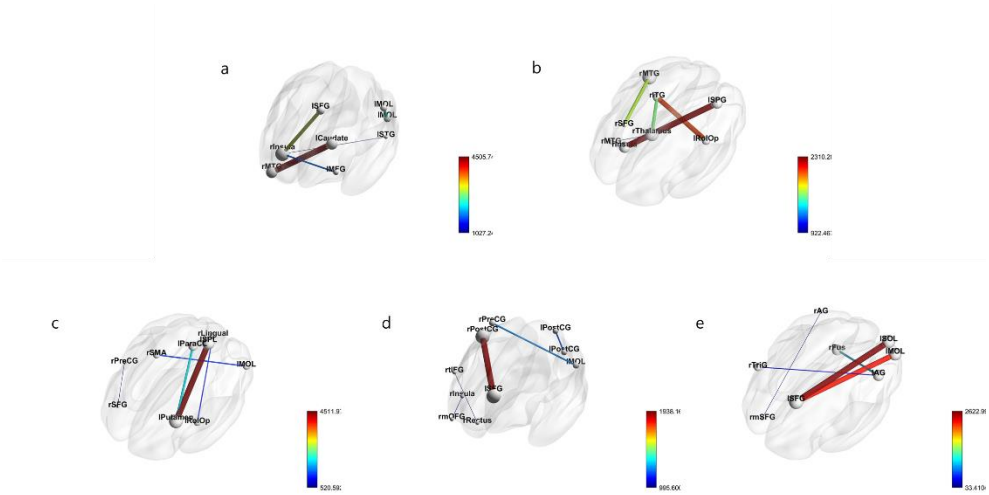

Figure 4. Top five influential edges in the construction of CPM models with significant predictive power

Table 13. Connectivity-based prediction models for negative prediction networks

Symptom clusters	Affective symptoms						Motivational symptoms				Somatic symptoms			
GDS subgroups	Core depressive symptoms		Lack of pleasure		Lack of happiness		Agitation		Withdrawal		Cognitive inefficiency		Lack of motivation	
Cognitive tests	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Episodic memory														
Recall index	-.03	-	.05	-	.43	.006	-.02	-	-.06	-	.09	-	.01	-
Recognition index	.16	.218	-.05	-	.26	.084	.15	.671	-.16	-	.08	-	.23	.103
Semantic memory														
Vocabulary	.22	.118	.39	.007	NaN	NaN	.18	.173	.15	-	-.15	-	.29	.041
Processing speed														
TMT A	.18	.095	.01	-	-.02	-	.01	-	.17	.83	-.18	-	-.18	-
Executive functions														
K-CWST	.11	-	-.02	-	.28	.053	.02	-	-.33	-	-.01	-	-.15	-
COWAT animal	-.13	-	.18	.157	.26	.08	-.12	-	-.08	-	.13	-	.09	-
COWAT store	.18	.165	-.46	-	-.25	-	-.06	-	.05	-	.29	.053	.32	.032
Working memory	-.01	-	-.18	-	-.15	-	-.08	-	-.15	-	-.09	-	.06	-

Table 14. Connectivity-based prediction models for positive prediction networks

Symptom clusters	Affective symptoms						Motivational symptoms				Somatic symptoms			
GDS subgroups	Core depressive symptoms		Lack of pleasure		Lack of happiness		Agitation		Withdrawal		Cognitive inefficiency		Lack of motivation	
Cognitive tests	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Episodic memory														
Recall index	-.17	-	-.19	-	-.09	-	.05	-	-	-	-.19	-	-.22	-
Recognition index	-.32	-	.04	-	-.26	-	-.10	-	-.29	-	.02	-	.27	.07
Semantic memory														
Vocabulary	-.37	-	-.55	-	.09	-	-.03	-	-.37	-	-.23	-	.12	-
Processing speed														
TMT A	.02	-	-.27	-	NaN	NaN	-.22	-	-.26	-	.26	.043	NaN	NaN
Executive functions														
K-CWST	-.06	-	-.18	-	NaN	NaN	-.18	-	.08	-	-.25	-	-.33	-
COWAT animal	-.31	-	-.09	-	-.09	-	.22	.108	.24	.099	-.05	-	NaN	NaN
COWAT store	-.15	-	-.14	-	.06	-	.26	.083	-.19	-	-.34	-	-.18	-
Working memory	.14	-	.13	-	NaN	NaN	.04	-	-.03	-	.02	-	.03	-

Table 15. Top five influential edges in predictive models

Symptom clusters	Affective symptoms		Somatic symptoms		
Predictive models	Lack of pleasure - Vocabulary	Lack of happiness - recall	Cognitive inefficiency – TMT A	Lack of motivation – Vocabulary	Lack of motivation – COWAT-s
Influential edges	R insula – L PHG	L tIFG – L caudate	L putamen – L SPL	L PostCG – L PostCG	L SFG – L SOL
	R insula – L PostCG	L SMG – L SFG	L putamen – L paraCG	L MOL – R PreCG	L SFG – L MOL
	L IPL – L Heschl's	R precuneus – L rOP	L MOL – R SMA	R insula – R mOFC	L FFG – L AG
	R insula – L SMG	R PreCG – L SMG	R PreCG – R SFG	L SFG – R PostCG	R tIFG – L AG
	R insula – L ACC	R PreCG – L SMG	L rOP – R LG	R rectus – R tIFG	R AG – R mSFG

* PHG = parahippocampal gyrus; PostCG = postcentral gyrus; IPL = inferior parietal lobe; Heschl's = Heschl's gyrus; SMG = supramarginal gyrus; ACC = anterior cingulate cortex; tIFG = pars triangualris of the inferior frontal gyrus; SFG = superior frontal gyrus; rOP = Rolandic operculum; PreCG = precentral gyrus; SPL = superior parietal lobe; paraCG = paracentral gyrus; SOL = superior occipital lobe; MOL = middle occipital lobe; SMA = supplementary motor area; LG = lingual gyrus; mOFC = medial orbitofrontal cortex; FFG = fusiform gyrus

Chapter 4. Discussion

This study investigated the heterogeneous relationship between distinct depressive symptom clusters and performance in cognitive domains in the healthy elderly population. There are two main findings that partially support the hypotheses proposed. First, in the behavioral level, there were no statistically significant associations between depressive symptom clusters and cognitive domains that survived correction for multiple comparisons. However, there were heterogeneous cognitive profiles associated with each symptom cluster when predicting neuropsychological performance with the resting state neural correlates of the symptom subgroups. Affective symptoms were associated with episodic and semantic memory, motivational symptoms were marginally associated with executive functions, and somatic symptoms were associated with semantic memory, processing speed and executive functions.

4.1. Heterogeneity in cognitive domains predicted by neural correlates of depressive symptoms

The most important result of the current study is that differential patterns in the prediction of cognitive performance in each symptom cluster were observed. Namely, there was a clear difference in the cognitive domains successfully predicted by rs-fc networks reflecting affective versus somatic symptoms; resting-state connections reflecting affective symptoms predicted performance related to memory, whereas connections reflecting somatic symptoms additionally predicted performance in tasks probing processing speed and fluency. Although there were no significant

associations between depressive symptoms and cognitive performance in the behavioral level, these results add to the current literature by bringing in implications for the neural underpinnings that may be functioning as biological mechanisms that can explain the heterogeneous relationship between depressive symptom clusters and cognitive function domains.

Affective symptoms and memory. In the current study, strong predictive models were produced for the lack of pleasure and Vocabulary and the lack of happiness and recall, and a marginally significant model was produced for the lack of happiness and recognition.

Compared to processing speed and executive functions, episodic memory has been reported to be inconsistently associated with depressive symptoms in both clinical and subclinical symptoms of LLD (Rashidi-Ranjbar et al., 2020; Sexton et al., 2012). Perhaps this is because episodic memory is a cognitive domain that is predominantly linked with affected symptoms that manifest in LLD. Indeed, episodic memory is a mental capacity that is well known to be influenced by emotion (Hamann, 2001). This relationship may have been obscured in previous studies probing the relationship between LLD and episodic memory due to the inclusion of other non-affective symptoms.

Another possible explanation is that the indices used in the current study strongly reflect the retrieval of episodic memory, rather than encoding. Encoding is reported to rely on neural correlates that differ from retrieval – the former being associated with prefrontal or frontotemporal circuits, and the latter with temporal regions, including the hippocampus (Shallice et al., 1994; Tulving & Markowitsch, 1998). Using measures that reflect encoding capacity such as items recalled from the first trial of word learning tasks, future studies can confirm this hypothesis of the

differentiative effect of the resting-state neural correlates of affective symptoms of LLD on encoding and retrieval of episodic memory.

Semantic memory is relatively less explored in the context of LLD. A recent study comparing cognitively intact community-dwelling older adults with and without depressive symptoms suggests that the overall severity of depressive symptoms is associated with a decline in semantic memory performance (Faoro & Hamdan, 2021). The results of the current study add to this finding in that affective symptoms in particular may play a role in the association between depressive symptoms and semantic memory in healthy older adults. However, further research must be conducted in order to confirm this relationship.

Somatic symptoms and semantic memory. Predictive models utilizing connectivity data related to the lack of motivation subgroup predicted performance in the Vocabulary task. The lack of motivation subgroup contains items of the GDS that ask about the level of somatic energy that one experiences, which may lead to difficulty in engaging in and sustaining adequate performance in activities that require effort. This may cause impairments in effortfully retrieving information stored in semantic memory (Lehrner et al., 2017), leading to poor performance in semantic memory tasks.

Somatic symptoms and non-memory domains. In the somatic symptom cluster, both the cognitive inefficiency subgroup and motivation subgroup yielded significant and marginally significant predictive models for TMT A and verbal fluency tasks. Although the verbal fluency tasks were used to measure the domain of flexibility within the larger category of executive functions in this study, they have been reported to additionally depend on processing speed and attention (Van der Elst et al., 2005). Thus, it can be suggested from this study that alterations in processing

speed, inferred through performance in the TMT A and two COWATs, is characteristic of the somatic symptom cluster of LLD.

However, it may also be that the somatic symptom cluster is associated with both processing speed and executive functions. A recent study on elderly patients with vascular disease experiencing subjective cognitive decline (SCD) reports that the level of SCD is associated with poorer performance in both processing speed and executive functions (Blom et al., 2019). Moreover, the lack of effortful engagement in tasks may cause difficulty in performing the particular tasks used to measure the two cognitive domains in this study (i.e., TMT A and word fluency tasks), which are known to require sustained attention (Park & Chey, 2003; Kang et al., 2012).

This result may possibly support the notion that executive functions are the "core deficits" of LLD (Herrmann et al., 2007; Sheline et al., 2006). Somatic symptoms have been reported to be prominent compared to other symptom domains in older depressed patients (Hegeman, Kok, et al., 2012). The executive dysfunction that is associated with this symptom domain may thus seem more accentuated when depressive symptoms are viewed as a whole, as had been for most previous studies regarding the relationship between depressive symptoms and cognitive impairment.

4.2. The neural underpinnings of symptom – cognition associations

The influential edges selected for the construction of the predictive models can be interpreted as neural correlates that underlie the link between depressive symptom clusters and cognitive impairment. As with previous literature on the neural underpinnings of impaired cognition in depression, the influential edges included

many connections between the frontolimbic areas of the brain (i.e., nodes including the insula, parahippocampal gyrus, ACC, caudate, and putamen) (Bohr et al., 2012; Greicius et al., 2007; Kenny, 2010; Li et al., 2017; McLaren et al., 2016; Tadayonnejad & Ajilore, 2014).

Affective symptoms and episodic memory. It is notable that a study by Bäckman et al. (1996) on an elderly community sample implies that rather than affective symptoms, motivational symptoms are related to a decline in performance in episodic memory, possibly due to their effect on abilities required to successfully encode information (i.e., sustained attention, maintaining interest in the task). Such incongruence may be explained through the underlying neural substrates of affective symptoms rather than behavioral data.

The head of the caudate is repeatedly reported to be related to executive functions in LLD (Bohr et al., 2012; Jayaweera et al., 2016; Naismith et al., 2012; Tadayonnejad & Ajilore, 2014). However, in this study, only the predictive model for the lack of happiness and recall featured a connection involving the caudate as an influential edge. This result is in tandem with a previous study reporting that the decreased volume of the caudate predicted poor memory function in patients with major depressive disorder, but not healthy controls (Jayaweera et al., 2016). These differential results on the role of the caudate in cognitive impairment in LLD may come due to the lack of acknowledgement of the heterogeneity of depressive symptoms. In other words, it may be that the caudate appears to have a different role in impairments in cognitive domains depending on the context of the specific symptom of depression.

Another highly implicated region especially in affective symptoms was the left supramarginal gyrus (SMG). This region is part of the inferior parietal lobule,

aligned with the angular gyrus, and is known to have a primary function in language processing. The right hemispheric SMG is also recognized to be associated with empathy (Silani et al., 2013). However, to date, no studies imply the role of the left SMG in emotional or memory-related functions. In this study, connectivity between the left SMG and right precentral gyrus was prominent both in the predictive model for recall by the lack of happiness, and a similar pattern occurred in the marginally significant predictive model for recognition (Table 16). Although there is a dearth of research on the role of the left SMG or its functional connections in the context of cognition in depression, one study reports that the SMG and pre/postcentral gyri were included in an extensive brain network associated with long-term meditation (Tomasino et al., 2013). This may imply that the connectivity between these two regions implicated in the predictive models for recall and recognition may indicate introspection that is required to retrieve memories.

Semantic memory. The prediction of Vocabulary by neural correlates of the lack of pleasure subgroup was highly influenced by right insular connections with limbic areas. The connection between the insula and the left postcentral gyrus, which is normally known as the somatosensory cortex, was unexpected. However, one study implies that the postcentral gyrus, along with the precentral gyrus, is related to higher cognitive tasks including working memory, mental rotation, and emotion regulation (Tomasino & Gremese, 2016). Another study postulates that hyperactivation in these regions are associated with the presence of depression in adolescents (Tsujii et al., 2017).

Although not implicated as nodes connected to the insula, influential edges in the predictive model for the motivation subgroup and Vocabulary predominantly included postcentral gyri in both hemispheres. This implies that the lack of pleasure

Table 16. Top five influential edges in marginally significant predictive models

Symptom clusters	Affective symptoms		Motivational symptoms	Somatic symptoms	
Predictive models	Lack of happiness - recognition	Lack of happiness – K-CWST	Agitation – COWAT-s	Cognitive inefficiency – COWAT-s	Lack of motivation – recall
Influential edges	L rOP - L LG	L vACC – L MCC	R SOL – L LG	L mSFG – L SPL	L vACC – L LG
	L SMG - L vACC	L IPL – R precuneus	R SOL – L SPL	L ITG – L ITG	L SFG – L LG
	L SMG - L SFG	L vACC – R PreCG	R mOFC – L PostCG	L mSFG – L paraCG	R ACC – L MOL
	L SMG - R PreCG	L MOL – R PreCG	R MFG – L PreCG	R paraCG – L paraCG	L STG – L SMG
	L SMG - R PreCG	L SMA – R PreCG	R ITG – R PreCG	L paraCG – R PreCG	R SMA – R IOL

* rOP = Rolandic operculum; LG = lingual gyrus; SMG = supramarginal gyrus; vACC = ventral anterior cingulate cortex; SFG = superior frontal gyrus; PreCG = precentral gyrus; MCC = middle cingulate cortex; IPL = inferior parietal lobe; MOL = middle occipital lobe; SOL = superior occipital lobe; SPL = superior parietal lobe; mOFC = medial orbitofrontal cortex; PostCG = postcentral gyrus; MFG = middle frontal gyrus; ITG = inferior temporal gyrus; paraCG = paracingulate gyrus; mSFG = medial superior frontal gyrus; IOL = inferior occipital lobe

subgroup and lack of motivation subgroup may share common neural mechanisms that influence semantic memory. Both subgroups are characterized by items that are related to apathy or fatigue (e.g., “Do you often get bored?”, “Do you feel full of energy?”). The overlap of nodes constituting the influential edges for predictive modeling in the two subgroups corroborate the postulation that the two subgroups may be reflecting different expressions of a common neural phenotype. However, since there is a lack of research on the neural mechanisms under the relationship between depressive symptoms and semantic memory in the older adult population, further research is required to confirm this hypothesis.

Somatic symptoms and processing speed. Neural correlates of somatic symptoms that accounted for model construction in TMT A and the COWATs supported previous literature on the underlying neural mechanisms for processing speed deficits in LLD. The putamen and superior frontal gyrus (SFG) each were key nodes among the influential edges for models predicting TMT A with cognitive inefficiency and COWAT-s with lack of motivation. These results support a regional homogeneity study reporting decreased homogeneity in the two frontocortical areas being associated with poorer performance in TMT A and B, which were each used as indices of processing speed and mental flexibility (Yuan et al., 2008). These results also support a speculation that decreased processing speed is a key feature in “vascular depression”, where subcortical microvascular lesions are prominent (Aizenstein et al., 2016; Herrmann et al., 2007).

Somatic symptoms and executive function. Classical theories on the neural underpinnings of cognitive impairment in LLD are based on the striatal-limbic hypothesis of executive dysfunction (Alexopoulos, 2002; Mayberg, 1997). This model postulates that impaired executive function in LLD is a result of a disruption

in the frontal-striatal-limbic networks. According to the model, "disconnection syndromes" that disrupt the interaction between regions within the network would result in problematic symptoms. Several past studies provide strong evidence for this hypothesis. Stronger rs-fc between the CCN and insula was reported to be associated with poorer executive function (Li et al., 2017), and greater regional homogeneity in the ACC was relevant to worse performance in set shifting and working memory (Respino et al., 2020). In an extensive review of the cognitive consequences of LLD, frontal regions (i.e., OFC, dlPFC, ACC, and SFG) and subcortical regions (i.e., thalamus, caudate, and putamen) involved in the limbic system were reported to be associated with a change in executive functioning (Naismith et al., 2012). However, influential edges in models that predict executive functions in this study show more of a frontoparietal pattern. This incongruence may be largely due to the fact that the population of interest consisted of healthy, nondemented and nondepressed older adults. This suggests that subclinical levels of depressive symptoms in healthy older adults may go through a distinct neural mechanism that links them to mild executive dysfunction.

In addition, the left superior frontal gyrus (SFG) was strongly implicated in the predictive model of the lack of motivation subgroup and executive function. The SFG is reported to influence emotional processing in younger adults with subclinical depression (Zhang et al., 2021), and cortical thinning in this area has been observed in patients with major depressive disorder (Wu et al., 2020). The result of this study agrees with previous accounts that the SFG has a role in cognitive control (Li et al., 2013), and thus it can be suggested that aberrant connectivity between the SFG and other regions of the brain may serve as an explanation as to what neural correlate links symptoms related to a lack of energy to executive dysfunction.

Possibility for alternative explanations. In addition to extracting rs-fc data that are associated with depressive symptoms and observing connections that influenced CPM model construction, connectivity data that are associated with performance in each neuropsychological task were extracted (Supplementary 2). However, there were very few overlaps among the strongest connections that represent depressive symptom subgroups and cognitive performance, and the few common connections were not implicated in the most influential edges for constructing predictive models. This implies that the neural correlates of depressive symptoms are not likely to be a direct neural mechanism of cognitive impairment. Rather, these neural correlates may be associated with poorer cognitive performance through a peripheral mechanism. For example, neural correlates of affective symptoms may negatively influence emotional processing, which in turn hinders the retrieval of episodic memory (Hitchcock et al., 2017). Further research is warranted in order to confirm this hypothesis.

4.3. Heterogeneity within affective symptoms

One interesting result of the current study was that the cognitive profile shown in the affective symptom cluster was different between the core depressive symptom subgroup and the lack of pleasure/happiness subgroups. In CPM, the neural correlates of the core depressive symptom subgroup did not produce any significant or marginally significant models, while the neural correlates of the lack of pleasure and lack of happiness subgroup each strongly predicted performance in the Vocabulary task and recall. Thus, it can be said that the neural correlates of the lack

of pleasure/happiness subgroups both predict long-term memory. However, the top five influential edges in predictive models between the lack of pleasure subgroup and Vocabulary, and the lack of happiness subgroup and recall did not show a strong overlap. Prediction for Vocabulary was strongly influenced by connections between the insula and limbic system (i.e., parahippocampal gyrus, ACC, and supramarginal gyrus), while prediction for recall was strongly influenced by connections between the suparamarginal gyrus and frontal areas (i.e., the pars triangularis of the IFG, SFG, and precentral gyrus). Nevertheless, the aforementioned regions are reported to be associated with emotional regulation and cognitive control (Li et al., 2013; Zhang et al., 2021), and thus it can be proposed that the two models share similar neural underpinnings in terms of neural functioning.

This division of the core depressive symptom subgroup, reflecting negative affectivity, and the lack of pleasure/happiness subgroup, reflecting the absence of positive affectivity, is congruent with clinical studies that postulate that the two types of affectivity in depression are differently expressed. This is supported by the subscale structure of the CES-D, which differentiates negative and positive affectivity, and a factor analysis study that divides the short form of the GDS into negative versus positive affectivity (Turner et al., 2015). In addition, the Minnesota Multiple Personality Index-II (MMPI-II; Graham, 2006), a widely used self-report scale that probes stable psychological qualities of an individual, also utilizes a validated set of reconstructed scales that split the construct of negative emotion from the lack of positive emotion, each implied in the RCd and RC2 subscales. Combined with the past literature, the current study thus supports that negative affectivity is not equivalent to the lack of positive affectivity in the context of depressive symptoms, even in the subclinical population.

4.4. Implications and future directions

Recently, there has been a growth of LLD literature that acknowledge the gravitas of considering the heterogeneity of depressive symptoms when studying their influence on cognitive functions (Korten et al., 2014). In addition to emphasizing the importance of considering the heterogeneity of symptoms when managing subclinical levels of depression in older adults, this study adds to this trend in three main ways.

First, this study was the first to include semantic memory to observe differential cognitive profiles in relation to depressive symptoms. Strong models were produced when predicting performance in the Vocabulary task in relation to symptom subgroups involving apathy and fatigue, therefore encouraging further research on how these specific symptom domains, rather than depression as a whole, may impact semantic memory. Because semantic memory is reported to be a risk factor of developing Alzheimer's dementia in patients with amnestic mild cognitive impairment (Estévez-González et al., 2004; Gainotti et al., 2014), further studies in this direction may bring about important findings about how apathy and fatigue may accelerate this process.

Moreover, unlike the majority of the existing literature on LLD's cognitive consequences, this study controlled for the influence of education. Education is well known as a proxy for cognitive reserve (Stern, 2009), exerting protective effects on cognitive impairment in old age (Brayne & Calloway, 1990). Years of education is also reported to dampen the negative impact of depression on cognitive functioning in elderly women (Lee et al., 2018) and the subclinical population (McLaren et al., 2015). Hence, the amount of formal education that an individual has received has the

potential to become a confounding factor in studies that investigate the relationship between LLD and its cognitive consequences. By considering the possible confounding role of education in analysis, the results of this study may provide a more accurate account on the relationships between depressive symptom clusters and cognitive domains.

Most importantly, this study is characteristic in that it investigates the healthy, community-dwelling population. Many previous studies implicate a significant influence of subclinical depressive symptoms on cognitive functions in the elderly. However, to date, only one study reports the underlying neural mechanisms for the relationship between depressive symptoms and cognitive dysfunction in the healthy population, including both younger and older adults (Dotson et al., 2014). The findings of this study are significant in they suggest the underlying neural mechanisms of the negative association between depressive symptoms and cognitive functions exclusively in the elderly population. Because depressive symptoms and cognitive aging are reported to produce interactive negative effects on functional outcome (Rao et al., 2015; Weisenbach & Kumar, 2014), the findings of this study may serve as an insight as to how subclinical depressive symptoms can affect the trajectory of cognitive aging.

One limitation of this study is that it did not control for the effects of vascular complications. The association between cognitive decline and vascular factors in LLD is well established (Baldwin et al., 2004; Thomas, 2004). Future studies may include smoking status, hypertension, heart disease status, or diabetes-related indices as controlling factors in order to confirm the validity of the current study (Charlson et al., 1987). Another limitation pertains to the unique demographic features of the participants in this study. The participants were recruited from closely neighboring

rural towns, where the community is characterized by tight social relationships between individuals. Social support and social network characteristics are known to mitigate the negative effects of depressive symptoms (Blazer, 2005; Olagunju et al., 2015) and moderate the relationship between depressive symptomology and cognitive functions (Kim et al., 2019). Thus, in order to confirm the generalizability of the current study, future studies should incorporate older adults with different social support characteristics, possibly by recruiting older adults from regions where social bonds are less prominent.

Supplementary Material

Supplementary 1. The symptom subscales and clusters of the GDS

Symptom cluster	Item
Affective symptoms	8. Are you afraid that something bad is going to happen to you? 13. Do you frequently worry about the future? 17. Do you feel pretty worthless the way you are now? 18. Do you worry a lot about the past? 24. Do you frequently get upset over little things? 25. Do you frequently feel like crying?
	3. Do you feel that your life is empty? 4. Do you often get bored? 10. Do you often feel helpless? 22. Do you feel that your situation is hopeless?
	5. Are you hopeful about the future? 7. Are you in good spirits most of the time? 9. Do you feel happy most of the time? 15. Do you think it is wonderful to be alive now? 19. Do you find life very exciting?
Motivational symptoms	1. Are you basically satisfied with your life? 6. Are you bothered by thoughts you can't get out of your head? 11. Do you often get restless and fidgety? 29. Is it easy for you to make decisions?
	12. Do you prefer to stay at home rather than go out and do things? 28. Do you prefer to avoid social occasions?
Somatic symptoms	14. Do you feel you have more problems with memory than most? 20. Is it hard for you to get started on new projects? 26. Do you have trouble concentrating? 30. Is your mid as clear as it used to be?
	21. Do you feel full of energy? 27. Do you enjoy getting up in the morning?
Undefined	2. Have you dropped many of your activities and interests? 16. Do you feel downhearted and blue? 23. Do you think that most people are better off than you are?

Items from Yesavage et al., 1987. Different symptom subgroups are differentiated with a solid line. They are in the order of: core depressive symptoms, lack of pleasure, lack of happiness, agitation, withdrawal, cognitive inefficiency, and lack of motivation.

Supplementary 2. Top 10 edges associated with each neuropsychological test

Recall index				
Region of interest	MNI coordinates	Region of interest	MNI coordinates	*T* (*df* = 148)
L thalamus	(-10, -18, 7)	L SPL	(-16, -46, 73)	-4.61
L thalamus	(-10, -18, 7)	L PostCG	(-38, -27, 69)	-4.52
R ITG	(46, -47, -17)	L rOP	(-38, -33, 17)	-4.43
R calcarine	(6, -81, 6)	R LG	(17, -91, -14)	-4.32
R tIFG	(53, 33, 1)	R LG	(20, -66, 2)	4.27
L PostCG	(-38, -27, 69)	R thalamus	(12, -17, 8)	-4.25
L SFG	(-20, 45, 39)	L ITG	(-42, -60, -9)	4.18
R SFG	(13, 30, 59)	R insula	(32, -26, 13)	-4.10
R FFG	(26, -79, -16)	L IFG	(-49, 25, -1)	4.10
L IOL	(-25, -98, -12)	R MCC	(5, 23, 37)	3.93

ITG = inferior temporal gyrus; tIFG = pars triangularis of the inferior frontal gyrus; PostCG = postcentral gyrus; SFG = superior frontal gyrus; FFG = fusiform gyrus; IOL = inferior occipital lobe; SPL = superior parietal lobe; rOP = Rolandic operculum; LG = lingual gyrus; IFG = inferior frontal gyrus; MCC = middle cingulum

Recognition index				
Region of interest	MNI coordinates	Region of interest	MNI coordinates	*T* (*df* = 147)
L SFG	(-20, 45, 39)	L ITG	(-42, -60, -9)	4.56
L MOL	(-26, -90, 3)	R LG	(18, -47, -10)	-4.37
R precuneus	(10, -62, 6)	L putamen	(-31, -11, 0)	-4.12
R STG	(52, -33, 8)	R SMG	(59, -17, 29)	4.07
R SFG	(31, 56, 14)	L AG	(-42, -55, 45)	-4.03
L LG	(-15, -72, -8)	L heschl	(-30, -27, 12)	-4.02
R ITG	(46, -47, -17)	L rOP	(-38, -33, 17)	-3.89
L paraCG	(-7, -21, 65)	R ITG	(58, -53, -14)	-3.87
R LG	(27, -97, -13)	L paraCG	(-13, -17, 75)	-3.83
L cuneus	(-3, -81, 21)	R SMG	(49, -42, 45)	3.83

SFG = superior frontal gyrus; MOL = middle occipital lobe; STG = superior temporal gyrus; LG = lingual gyrus; ITG = inferior temporal gyrus; paraGC = paracentral gyrus; SMG = supramarginal gyrus; AG = angular gyrus; rOP = Rolandic operculum

Vocabulary				
Region of interest	MNI coordinates	Region of interest	MNI coordinates	*T* (*df* = 148)
L MOL	(-24, -91, 19)	R SMA	(10, -17, 74)	-4.22
R ITG	(42, -66, -8)	L putamen	(-31, -11, 0)	4.07
R ITG	(58, -53, -14)	R rectus	(8, 41, -24)	-4.03
L MTG	(-56, -50, 10)	R postCG	(51, -6, 32)	3.99
R paraCG	(2, -28, 60)	R MOL	(6, 67, -4)	3.85
L MTG	(-58, -26, -15)	R insula	(36, 22, 3)	-3.77
R SMA	(10, -17, 74)	L vACC	(-14, -18, 40)	3.73
R SMG	(49, -42, 45)	L postCG	(-21, -31, 61)	-3.63
L MFG	(-35, 20, 51)	R preCG	(29, -5, 54)	3.62
R LG	(20, -66, 2)	R STG	(58, -16, 7)	-3.59

MOL = middle occipital lobe; ITG = inferior temporal gyrus; MTG = middle temporal gyrus; paraCG = paracentral gyrus; SMA = supplementary motor area; SMG = supramarginal gyrus; MFG = middle frontal gyrus; LG = lingual gyrus; postCG = postcentral gyrus; vACC = ventral anterior cingulate cortex; preCG = precentral gyrus; STG = superior temporal gyrus

TMT				
Region of interest	MNI coordinates	Region of interest	MNI coordinates	*T* (*df* = 148)
R MTG	(46, 16, -30)	L MTG	(-49, -42, 1)	-4.83
L MTG	(-49, -42, 1)	R precuneus	(10, -62, 6)	-4.08
R MTG	(46, 16, -30)	L MTG	(-58, -30, -4)	-4.06
R MTG	(46, 16, -30)	L MTG	(-56, -13, -10)	-3.99
R MTG	(46, 16, -30)	L preCG	(-38, -15, 69)	-3.8
R SMA	(10, -17, 74)	L STG	(-60, -25, 14)	3.75
R SFG	(13, 55, 38)	L SFG	(-20, 45, 39)	-3.74
L MTG	(-49, -42, 1)	R postCG	(29, -39, 59)	-3.73
R LG	(20, -86, -2)	L mPFC	(-2, 38, 36)	-3.69
R SMA	(10, -17, 74)	R ITG	(58, -53, -14)	3.66
R rOP	(56, -5, 13)	R ITG	(55, -31, -17)	3.65

MTG = middle temporal gyrus; SMA = supplementary motor area; SFG = superior frontal gyrus; LG = lingual gyrus; rOP = Rolandic operculum; preCG = precentral gyrus; STG = superior temporal gyrus; postCG = postcentral gyrus; mPFC = medial prefrontal cortex; ITG = inferior temporal gyrus

K-CWST				
Region of interest	MNI coordinates	Region of interest	MNI coordinates	*T* (*df* = 144)
L MCC	(-5, 18, 34)	L postCG	(-38, -27, 69)	-4.53
R thalamus	(12, -17, 8)	L preCG	(-53, 3, -27)	-4.50
R tIFG	(48, 25, 27)	R SMG	(54, -28, 34)	4.32
R thalamus	(9, -4, 6)	L SOL	(-14, -91, 31)	-4.28
R rectus	(8, 41, -24)	R tIFG	(53, 33, 1)	4.26
R thalamus	(9, -4, 6)	R SOL	(15, -87, 37)	-4.09
L SOL	(-18, 63, -9)	L postCG	(-49, -11, 35)	4.08
L PHG	(-21, -22, -20)	L MFG	(-23, 11, 64)	-4.02
R thalamus	(9, -4, 6)	R SMG	(49, -42, 45)	-3.93
R thalamus	(9, -4, 6)	R insula	(37, 1, -4)	-3.92
R thalamus	(9, -4, 6)	R SOL	(24, -87, 24)	-3.89

MCC = middle cingulate cortex; tIFG = pars triangularis of the inferior frontal gyrus; SOL = superior occipital lobe; PHG = parahippocampal gyrus; postCG = postcentral gyrus; preCG = precentral gyrus; SMG = supramarginal gyrus; MFG = middle frontal gyrus

COWAT animal				
Region of interest	MNI coordinates	Region of interest	MNI coordinates	*T* (*df* = 147)
L SMG	(-53, -22, 23)	R MCC	(5, 23, 37)	4.42
R ITG	(49, -3, -38)	R rOP	(56, -5, 13)	-4.07
R insula	(37, 1, -4)	R postCG	(42, -20, 55)	-3.95
L IOL	(-25, -98, -12)	R AG	(37, -65, 40)	-3.90
L SFG	(-20, 45, 39)	R insula	(36, 10, 1)	-3.80
L SPL	(-28, -58, 48)	R caudate	(15, 5, 7)	3.77
R preCG	(42, 0, 47)	R LG	(17, -91, -14)	-3.65
R MCC	(10, -2, 45)	R insula	(27, 16, -17)	3.65
R ITG	(49, -3, -38)	R ITG	(55, -31, -17)	-3.62
L putamen	(-31, -11, 0)	L FFG	(-47, -51, -21)	-3.58

SMG = supramarginal gyrus; ITG = inferior temporal gyrus; IOL = inferior occipital lobe; SFG = superior frontal gyrus; SPL = superior parietal lobe; preCG = precentral gyrus; MCC = middle cingulate cortex; rOP = Rolandic operculum; postCG = postcentral gyrus; AG = angular gyrus; LG = lingual gyrus; FFG = fusiform gyrus

COWAT store				
Region of interest	MNI coordinates	Region of interest	MNI coordinates	*T* (*df* = 148)
R MCC	(10, -2, 45)	L MCC	(-5, 18, 34)	-4.59
R thalamus	(6, -24, 0)	L MCC	(-1, 15, 44)	-4.27
L FFG	(-47, -51, -21)	R rOP	(56, -5, 13)	4.19
R insula	(36, 10, 1)	R insula	(32, -26, 13)	-4.08
L postCG	(-40, -19, 54)	L MCC	(-5, 18, 34)	-3.89
R postCG	(20, -29, 60)	L postCG	(-38, -27, 69)	-3.77
R MFG	(40, 18, 40)	R LG	(27, -97, -13)	-3.77
L MOL	(-40, -88, -6)	R postCG	(66, -8, 25)	-3.76
R MTG	(51, -29, -4)	L MCC	(-5, 18, 34)	-3.75
R thalamus	(6, -24, 0)	R iOFC	(49, 35, -12)	-3.75
R IPL	(47, -30, 49)	R sOFC	(24, 45, -15)	-3.74
L postCG	(-40, -19, 54)	R ACC	(10, 22, 27)	-3.73
L IPL	(-39, -75, 44)	L ACC	(-3, 42, 16)	-3.73
L postCG	(-38, -27, 69)	L MCC	(-5, 18, 34)	-3.73

MCC = middle cingulate cortex; FFG = fusiform gyrus; postCG = postcentral gyrus; MFG = middle frontal gyrus; MOL = middle occipital lobe; MTG = middle temporal gyrus; IPL = inferior parietal lobe; rOP = Rolandic operculum; LG = lingual gyrus; iOFC = inferior orbitofrontal cortex; sOFC = superior orbitofrontal cortex; ACC = anterior cingulate cortex

Working Memory				
Region of interest	MNI coordinates	Region of interest	MNI coordinates	*T* (*df* = 148)
L paraCG	(-7, -33, 72)	L insula	(-35, 20, 0)	-4.42
L SFG	(-10, 55, 39)	R MCC	(10, -2, 45)	4.25
R MOL	(6, 67, -4)	L paraCG	(-7, -21, 65)	4.23
R postCG	(20, -29, 60)	L postCG	(-38, -27, 69)	-4.17
L postCG	(-21, -31, 61)	L postCG	(-38, -27, 69)	-4.09
L paraCG	(-7, -33, 72)	L mSFG	(-3, 26, 44)	-3.96
R MOL	(6, 67, -4)	L paraCG	(-7, -33, 72)	3.96
L postCG	(-53, -10, 24)	R MTG	(52, -2, -16)	3.95
L iOP	(-47, 11, 23)	L insula	(-31, 19, -19)	-3.93
R postCG	(66, -8, 25)	L rOP	(-45, 0, 9)	3.91
L paraCG	(-7, -33, 72)	R OFC	(34, 38, -12)	-3.85

paraCG = paracentral gyrus; SFG = superior frontal gyrus; MOL = middle occipital lobe; postCG = postcentral gyrus; iOP = inferior operculum; MCC = middle cingulate cortex; mSFG = medial superior frontal gyrus; MTG = middle temporal gyrus; rOP = Rolandic operculum; OFC = orbitofrontal cortex

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노년기 우울 증상들의 신경상관자가 인지기능에 미치는 서로 다른 예측성

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노년기 우울장애는 그 증상만으로도 노인의 인지기능에 부정적인 영향을 미친다는 점에서 고령화가 가속화되는 현대 사회에서 중요하게 다뤄져야 하는 주제이다. 그러나 임상적인 수준에 다다르지 않은 건강한 인구에서 이질적인 우울 증상이 서로 다른 영역의 인지기능에 미치는 영향의 기저에 있는 신경적인 기전에 대한 연구는 상대적으로 미비하다. 따라서 이 연구는 우울의 정서적, 동기적, 그리고 신체적 증상을 구분하여, 각각의 증상군의 신경상관자가 노인의 일화기억, 의미기억, 처리속도, 그리고 집행기능의 예측에서 갖는 역할을 탐색하고자 했다. 157명의 건강한 노인을 모집하여 한국판 노년기 우울척도(GDS), 신경심리검사, 그리고 휴지기 기능적 뇌영상촬영을 진행했다. GDS의 문항은 선행연구에 따라 일곱 가지의 하위 증상군으로 분류되었고, 차례로 세 가지의 큰 증상 클러스터로 묶였다. 일화기억, 의미기억, 처리속도, 그리고 집행기능은 노인 우울장애 검사, 어휘 과제, 선로 잇기 검사, 스트룹 검사, 그리고 언어 유창성 검사를 이용하여 측정하였다. 우울 증상에 따른 인지기능 패턴의 변화에 대한 선행연구 결과를 재검증하기 위해 하위 증상군 점수와 인지검사 점수를 각각 독립변수와

종속변수로 둔 선형회귀모델을 구성하였다. 또한 각 참가자에 대해 일곱 개의 하위 증상군 수준을 반영하는 기능적 연결 행렬(FC 행렬)을 구성하여, 각 인지기능 점수에 대한 연결성-기반 예측적 모델링을 하는 데에 이용하였다. 마지막으로 통계적으로 유의미한 예측모델에 대해, 모델의 구성에 있어 가장 큰 영향을 미친 FC 행렬의 에지(edge)를 구하였다. 행동 데이터에 대해서는 유의미한 결과가 도출되지 않았지만, 연결성-기반 예측적 모델링의 결과, 정서적 증상에 대한 신경상관자는 일화기억과 의미기억을, 그리고 신체적 증상에 대한 신경상관자는 의미기억, 처리속도, 그리고 집행기능을 예측했다. 즉, 이 연구는 세 우울 증상 클러스터와 여러 인지기능 영역에 대한 서로 다른 관계의 신경적인 기전에 대한 증거를 제시하고 있다. 또, 이 연구는 건강한 노인을 대상으로 하고 있으므로, 임상적인 수준 이하의 우울 증상이 노화에 따른 인지적 저하의 추세에 영향을 미칠 수 있다는 함의를 갖는다.