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Review article

Fifteen years of NESDA Neuroimaging: An overview of results related to clinical profile and bio-social risk factors of major depressive disorder and common anxiety disorders

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ABSTRACT

The longitudinal Netherlands Study of Depression and Anxiety (NESDA) Neuroimaging study was set up in 2003 to investigate whether neuroanatomical and functional abnormalities during tasks of primary emotional processing, executive planning and memory formation, and intrinsic brain connectivity are *i)* shared by individuals with major depressive disorder (MDD) and common anxiety disorders; and *ii)* characterized by symptomatology-specific abnormalities. Furthermore, questions related to individual variations in vulnerability for onset, comorbidity, and longitudinal course could be investigated.

Between 2005 and 2007, 233 individuals fulfilling a diagnosis of MDD, panic disorder, social anxiety disorder and/or generalized anxiety disorder and 68 healthy controls aging between 18 and 57 were invited from the NESDA main sample (n = 2981). An emotional faces processing task, an emotional word-encoding task, and an executive planning task were administered during 3T BOLD-fMRI acquisitions. In addition, resting state BOLD-fMRI was acquired and T1-weighted structural imaging was performed. All participants were invited to participate in the two-year and nine-year follow-up MRI measurement.

Fifteen years of NESDA Neuroimaging demonstrated common morphological and neurocognitive abnormalities across individuals with depression and anxiety disorders. It however provided limited support for the idea of more extensive abnormalities in patients suffering from both depression and anxiety, despite their worse prognosis. Risk factors including childhood maltreatment and specific risk genes had an emotion processing modulating effect, apparently stronger than effects of diagnostic labels. Furthermore, brain imaging data, especially during emotion processing seemed valuable for predicting the long-term course of affective disorders, outperforming prediction based on clinical information alone.

1. Introduction

Affective disorders including Major Depressive Disorder (MDD) and common anxiety disorders (panic disorder, social anxiety disorder, generalized anxiety disorder) are the most prevalent psychiatric disorders and are characterized by considerable heterogeneity in clinical presentation, etiology, and course of the disorders (Malhi and Mann, 2018). Not only is the symptom representation highly variable across individuals within a certain diagnostic category, this is also the case in terms of simultaneously fulfilling the criteria for multiple psychiatric or somatic diagnostic categories. Psychiatric comorbidity is especially high between MDD and anxiety disorders, most notably panic disorder (PD), social anxiety disorder (SAD), and generalized anxiety disorder (GAD) (Gorman, 1996). Comorbidity estimations vary between 10 and 50 per cent (Gorman, 1996; Roy-Byrne et al., 2000), and often the clinical manifestation of the anxiety disorder precedes the onset of the major depressive episode. Because of this high overlap, but also because depression and anxiety respond to the same treatment strategies (e.g. cognitive behavioral therapy and serotonin reuptake inhibitors), it has been suggested that they have overlapping neurobiological underpinnings, including shared abnormal structural and functional brain pathways (Ressler and Mayberg, 2007). In 2003, clinical neuroimaging

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studies were still very few in number and no study had investigated the overlap in structural and functional brain abnormalities associated with MDD and most common anxiety disorders. Also, existing studies in either depression or anxiety disorders were mostly based on small sample sizes, not allowing to control for, or specifically investigate, clinical heterogeneity. Finally, although it was known at the time that comorbidity of MDD and anxiety was associated with a less favorable clinical course, it was unknown if any structural or functional brain abnormalities would be associated with this clinical phenomenon and whether persistence of depression and anxiety would also be associated with 'aggravation' of brain abnormalities over time. These questions were the primary reason to set up a longitudinal Neuroimaging study as an add-on study of the Netherlands Study of Depression and Anxiety (NESDA) in 2003, in alignment with the main objectives of the main NESDA study (Penninx et al., 2008).

2. Design of NESDA Neuroimaging study

Between January 2005 and April 2007, 301 individuals from the NESDA cohort were included for a structural and functional MRI session at one of the participating centers: Amsterdam, Leiden, or Groningen, where a similar type of 3T Philips MRI scanner was operational. We invited participants who were scheduled for the NESDA baseline interview to also participate in the NESDA Neuroimaging study if they fulfilled the DSM-IV criteria for MDD, SAD, PD and/or GAD in the past 6 months, were available for a scanning session within eight weeks following the baseline interview, were not using any other antidepressant medication than selective serotonin reuptake inhibitors, and had non-regular use of benzodiazepines (see van Tol et al. (2010), for a full overview of in- and exclusion criteria for the NESDA Neuroimaging study). Severity of depressive and anxiety symptomatology was assessed again at the time of scanning We chose our functional MRI task-paradigms based on the then brand new neurocognitive model of Mary Philips on the trans-diagnostic importance of emotional processing for psychiatric disorders (Phillips et al., 2003a, 2003b) and the related limbic-cortical neuroanatomical model of depression of Helen Mayberg (1997), both stressing the importance of adequate interaction between 'dorsal' cortical brain areas and 'ventral' limbic brain regions. We administered the parametric Tower of London executive planning task (van den Heuvel et al., 2003) to capture activity in a 'dorsal' executive control network, an emotional face processing task including sad, fearful, angry, happy and neutral facial pictures (adapted from Wolfensberger et al., 2008) to capture activity of a 'ventral' primary emotional processing network, and an emotional implicit word-encoding and -recognition task (Daselaar et al., 2003; de Ruiter et al., 2007) to capture activity in a memory network. Furthermore, following the promising, at the time new insights that resting state functional connectivity could bring (Damoiseaux et al., 2006; Greicius et al., 2007; Raichle et al., 2001), we included an 8-minute resting state BOLD-fMRI acquisition after individuals were instructed to close their eyes and not think of anything in particular[1]. Finally, a 3D-T1 weighted structural image was acquired for volumetric quantification. The order of the acquisitions was 1) BOLD-fMRI during Tower of London, 2) BOLD-fMRI during implicit encoding of emotional words, 3) T1-3D, 4) BOLD-fMRI during recognition of emotional words, 5) BOLD-fMRI emotional faces task and 6) "resting-state" BOLD-fMRI.

At two-year follow-up, we repeated the full MRI-session and included 199 individuals of the original n=301 sample. The same tasks and sequences were employed. At this two-year follow-up, the 6-channel SENSE head coil in Amsterdam was replaced by an 8-channel SENSE head coil. Otherwise, scanner hardware was identical. At 9-year follow-up, we invited all participants who participated in the baseline measurement, and additionally invited 40 patients fulfilling criteria of MDD with a 6 months recency, 40 healthy siblings of participating MDD patients, and 15 additional healthy controls without a first or second degree family member with any psychological problems. This resulted in the inclusion of a total number of 98 MDD patients and 41 HC for the nine year follow-up measurement. During this assessment, a T1-3D structural image, a 10-minute resting state acquisition, a DTI-scan (Heij et al., 2019), and BOLD-fMRI during a task of effortful emotion regulation of positive and negative emotional images (van Kleef et al., in preparation) were acquired. This measurement was completed between September 2013 and September 2016. In Leiden, the 3T Philips Achieva system had been upgraded with a 32-channel SENSE head coil. At this time, the scanner in Amsterdam was being replaced, therefore most participants included in the Amsterdam area traveled to Leiden for their scan (only 30 minutes by train). In Groningen, the same Philips Intera system as during the baseline and two year follow-up was still operational, although now equipped with a 32- channel SENSE coil. See Fig. 1 for an overview of neuroimaging measurements and samples.

The NESDA MRI project was considered a medium to large scale psychiatric neuroimaging initiative at the time, but in the past decade neuroimaging (and genetics) initiatives of a completely different scale have been launched such as the ENIGMA project (Thompson et al., 2014) and the UK Biobank (http://www.ukbiobank.ac.uk/about-biobank-uk). As detailed below, the NESDA consortium is an active member of the global ENIGMA initiative in which data from the NESDA MRI are used in mega- and meta-analytic approaches.

3. Overview of primary and secondary NESDA Neuroimaging analyses

3.1. Comorbidity of depression and common anxiety disorders

One of the main aims of the NESDA study is to investigate depression and anxiety in concert and to integrate biological and psychosocial models of mood and anxiety disorders (see Penninx et al., 2008). We could therefore include patients with MDD, SAD, PD and/or GAD in the past 6 months for the NESDA imaging study. This allowed us to study whether functional and structural MRI-characteristics of individuals suffering from MDD differed from those suffering from an anxiety disorder, or those suffering from both MDD and a common anxiety disorder. The primary analyses focused on comparing groups of patients fulfilling either criteria for MDD (n = 70), anxiety disorders (n = 71), MDD and comorbid anxiety disorders (n = 92), and healthy controls (n = 68).

Structural imaging: Van Tol et al. (2010) showed in their whole-brain voxel-based morphometry (VBM) analysis of 298 high-quality structural T1-weighted scans that abnormally low volume of the pregenual to dorsal-anterior cingulate cortex was generically observable across individuals with MDD and anxiety disorders compared to healthy individuals, supporting the hypothesis of a common neuropathology. Though not included as *a priori* region of interest, anxiety-depression common lower volume of the posterior cingulate cortex was also observed. Disorder-class specific abnormalities were observed as well. Abnormally low volume of the right inferior frontal cortex was only present in individuals with MDD without comorbid anxiety whereas abnormally low volume of the left superior temporal gyrus was specific to individuals with only anxiety disorders. All observations were independent of sex, age, education, current severity of depressive and anxiety symptomatology, and use of antidepressant medication. Additionally, it was observed that MDD patients with an onset of their first episode before the age of 18 displayed lower subgenual anterior cingulate volume than patients who experienced their first depression after their 18th birthday. No effects for time of onset of the first anxiety episode were observed.

Executive planning: The analysis of whole brain voxel-based fMRI-

[1] Of note, the resting state sequence was added to the study 10 months after inclusion of the first participant and therefore was not available for all participants.

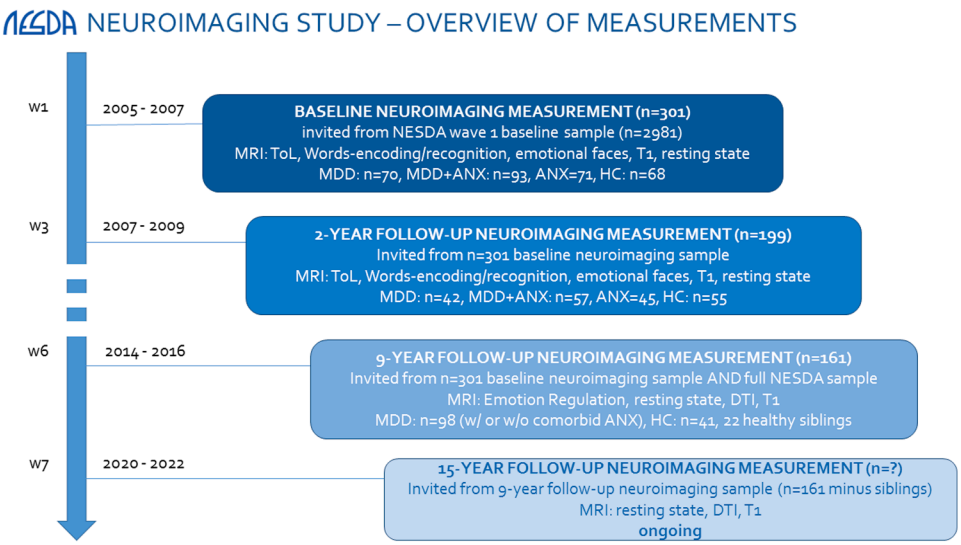

Fig. 1. Summary of NESDA Neuroimaging measurements at NESDA waves 1 (baseline), 3 (2-year follow-up), 6 (9-year follow-up) and 7 (15-year follow-up), including sampling base, type of tasks/MRI-measurements, and sample size per clinical/healthy group.

correlates of executive planning during performance of the parametric Tower of London visuospatial planning task in 211 patients and 63 healthy controls showed marginal support for the hypothesis of abnormalities in the prefrontal cortex associated with MDD symptomatology (van Tol et al., 2011). Analyses indicated slightly elevated activation as a function of increasing planning difficulty in the left dorsolateral prefrontal cortex, which was most pronounced in individuals fulfilling criteria for only MDD (n = 65) and showing moderate to severe depressive symptomatology of depression at the time of scanning. No abnormalities were observed in individuals fulfilling a diagnosis of anxiety disorders only (n = 64). Correction for age, education, sex, and anti-depressant medication use did not change these results. These results suggest that frontal over-recruitment during executive planning is a state characteristic of depression without anxiety.

Emotional face processing: Related to processing of angry, fearful, sad, happy, and neutral faces during a gender-discrimination task including stimuli from the Karolinska Directed Emotional Faces emotional faces set (Lundqvist et al., 1998), no support for abnormal 'ventral' limbic processing was observed in 182 patients with MDD and/or anxiety disorders in response to negative (fearful, sad, angry) face processing compared to healthy controls (n = 56) (Demenescu et al., 2011). Both amygdala response peak height (whole-brain voxel-based) and response shape (of the amygdala region of interest) were investigated. Also, no differences in activation of the amygdala were observed after excluding patients that used antidepressants or when taking current severity of depression or anxiety into account. Instead, hyperactivation of the right dorsolateral prefrontal gyrus in response to positive face viewing was observed in MDD patients, which was interpreted as reflecting an increased demand of resources needed to process the conflict between the stimulus valence and the current mood state. Patients with only anxiety disorders showed elevated responses to happy faces in the lentiform nucleus, explained as defective basal-ganglia linked reward processing previously associated with anxiety disorders. In a follow-up analysis focusing on type of anxiety diagnosis, abnormally low amygdala and lingual gyrus activation to angry, happy, fearful, and neutral faces was observed in PD patients, but not in SAD patients, compared to controls (Demenescu et al., 2013). Presence of co-morbid GAD did not affect this result. Furthermore, in these analyses, the class of anxiety disorder was not associated with abnormal amygdala-seeded connectivity with the medial prefrontal cortex, thought current severity of anxiety symptomatology as measured with the Beck Anxiety Index was associated with increased connectivity during viewing of fearful, but not happy or neutral faces across patients. This suggests that aberrant amygdala responsivity is not common to all anxiety disorders, and may explain the absence of a general anxiety effect in the analyses where all diagnostic classes were pooled. Furthermore, anxiety severity may relate to connectivity with regulatory medial prefrontal brain areas, while not impacting amygdala responsiveness per se.

Implicit word encoding: During the process of implicitly encoding emotional words, it was observed in a whole-brain voxel-wise analysis that patients with depression, anxiety disorders, or both showed abnormally low activation of the right medial hippocampus, which was interpreted as suggestive of abnormal contextual coupling of positive information underlying the vulnerability for both depression and anxiety (van Tol et al., 2012). During implicit encoding of negative words, a depression specific effect of insular hyperactivation was observed in MDD (with [n = 56] and without anxiety disorders [n = 51]) compared to patients with anxiety disorders (n = 56) and healthy controls (n = 49). In the acutely depressed state, additional hyperactivation of the ventrolateral prefrontal cortex and amygdala was observed during negative word encoding, suggesting increased call for attentional resources related to heightened salience detection of negative information. Furthermore, in the acutely depressed state, anterior cingulate cortex hyperactivation was observed during positive word encoding, which was interpreted as being reflective of conflict processing and the need for extra resources to classify mood-incongruent information.

Resting state functional connectivity: In a subset of unmedicated depressed and anxious patients, effects of comorbidity on resting state functional connectivity patterns in four networks of interest were investigated (Pannekoek et al., 2015). Using a probabilistic independent components analysis, group differences between patients with MDD (n = 37), anxiety disorders (n = 30), MDD and anxiety disorders (n = 25) and healthy controls (n = 48) were investigated in *i*) a limbic network encompassing the amygdala, basal ganglia and ventrolateral temporal cortex, *ii*) a salience network encompassing the insula and anterior cingulate cortex extending into the dorsomedial frontal gyrus, *iii*) a sensory-motor cortex encompassing the sensory-motor cortices, and iv) a default-mode network encompassing medial parietal and frontal brain regions. Analyses showed no effects specific to the presence of depression or anxiety. However, abnormal connectivity of the limbic network with posterior regions, including the precuneus and lingual gyrus, and right ventro- and dorso-lateral prefrontal regions was observed in the group of patients suffering from comorbid depression and anxiety

disorders. No effects of illness severity were observed. The authors interpreted the heightened coupling of the posterior visual and parietal regions with the limbic network as reflective of abnormal self-related cognitive processing, and the heightened lateral frontal limbic-network coupling as reflective of abnormal emotion detection present in depression and anxiety. It is important to note that in an earlier analysis connectivity differences were observed between 19 carefully selected unmedicated MDD patients without comorbidity and 19 matched controls. Results by Veer et al. (2010) showed abnormal lower connectivity of the bilateral amygdala with a limbic network, lower connectivity of the frontal poles to an attentional network, and lower connectivity of the lingual gyrus with a medial-visual network was observed. Subtle differences in selected cases, including the healthy controls, could explain the MDD-related non-overlapping results of Veer et al. (2010) and Pannekoek et al. (2015).

Surprisingly, the resting state functional connectivity findings reported by Pannekoek et al (2015) were the only comorbidity-specific finding in all NESDA neuroimaging data-analyses focusing on disorder-common vs. -specific characteristics of depression and/or anxiety disorders. Volumetric and task-related functional abnormalities were not specific to, or more pronounced in, the comorbid group compared to the non-comorbid groups, despite longer illness duration and severity of both depressive and anxiety symptomatology of the comorbid group. Together these findings give little support for the suggestion that functional and structural brain abnormalities are additive in a way that the symptomatology of MDD and anxiety disorders are. Overall, comorbid depression and anxiety seems most closely related to MDD without anxiety disorders, especially during the acutely depressive state. Findings specific for anxiety were observed as well, rarely shared with comorbid depression and anxiety and not with depression without comorbid anxiety. This suggests that anxiety related pathology is either anxiety vulnerability specific, or generically underpinning the vulnerability for affective disorders.

3.2. Course characteristics

Because of the longitudinal design of NESDA and the NESDA Neuroimaging study, questions related to state-dependency of MDD-related brain abnormalities could be addressed for the first time in the context of a naturalistic study where participants were not assigned to a specific treatment regime. This was one of the primary aims of setting up the longitudinal NESDA Neuroimaging study. Furthermore, because of the careful mapping of the course of the depressed psychopathology over a nine-year period and the completion of an MRI-measurement at nine-year follow-up, the relation between course of the depression and functional and structural brain characteristics could be prospectively studied.

Prediction of depressive course: It was observed that at baseline, MDD patients who would not remit in the two year follow-up period (n = 29) showed higher right hippocampal, left amygdala and left insular activation during the encoding of negative words than healthy controls (n = 45) (Ai et al., 2015). Hyperactivation in these regions was not observed in patients who would quickly remit after the baseline measurement (n = 22, remission within one year) or remit but relapse within two-years (n = 23). Also, irrespective of illness severity, right hippocampal activation during negative word encoding at the baseline measurement was found to positively relate to time to remission: the higher the activation, the longer it would take to reach remission. The authors concluded that higher activation in the left insula could serve as a neural marker of a naturalistic non-remitting course, whereas higher hippocampal activation is associated with delayed remission. Related to processing of emotional faces, higher rostral anterior cingulate activation during positive face processing at baseline was associated with symptomatic remission, compared to patient who would not remit over the two-year interval (Opmeer et al., 2016).

In addition to unimodal associations with clinical state a two-year follow-up, multimodal multi-variate pattern recognition was applied to investigate whether neuroimaging data could improve the prediction of the course of the depressive disorder over the use of known clinical predictors (including illness severity, duration and comorbidity) alone. Schmaal et al. (2015) grouped 118 MDD patients based on their clinical trajectory over the two-year period into chronically depressed patients (n = 23), gradually improving patients (n = 36), and fast remitters (n = 59). Using a Gaussian process classifier approach, it was shown that chronic patients could be discriminated from gradual recovering and fast remitting patients based on the emotional face processing fMRI-data with 73% accuracy, but not from structural MRI and fMRI related to executive planning. This accuracy was higher than predicting outcome from clinical data alone, which suggests that neural responses, especially during emotional processing tasks, could improve clinical outcome prediction. In a follow-up analysis, generative embedding was used to predict individual course trajectories based on the effective connectivity estimates derived from dynamic causal modeling of signal from the bilateral occipital face area, fusiform face area and the amygdalae during the emotional face processing task (Frässle et al., 2020). Using this approach, chronic patients could be distinguished from fast remitting patients with 79% accuracy. Gradually improving patients could be distinguished from fast remitting patients with 61% accuracy. This predictive approach significantly outperformed more traditional approaches (i.e. support vector machine based classification) based on activation or functional connectivity of the regions of interest. This suggest that more elaborative prediction methods can even further improve prediction accuracy.

State-characteristics: Ai et al (2019) observed in 39 MDD patients that the difference in activation of the left anterior hippocampus, extending into the amygdala, between the baseline and two-year follow-up measurement during encoding of positive and negative words, increased when symptomatic change over the two-year period was larger. This increase in activation was suggestive of normalization. During processing of emotional faces, a decrease in activation of the bilateral anterior insula and amygdala was observed in patients who remitted over the two-year period, most notably during processing of positive faces (Opmeer et al., 2016). Additionally, an increase in activation of the parahippocampal gyrus extending to the fusiform gyrus, the dorsolateral prefrontal cortex, and the post-central gyrus during positive face processing was observed with remission during emotional face viewing. Results were independent of any therapy. These results suggest that activation of typical emotion processing areas, including the anterior hippocampus, amygdala and insula, but also areas associated with processing of social emotional cues, responds in a state-dependent manner, indicating activation in these areas may serve as treatment response markers.

Time spent with depression: Time spent with depression in the two-year interval following baseline was not associated with activation differences during emotional word encoding. This suggests that regional brain activation is not subject to 'functional scarring' owing to prolonged presence of depressive symptomatology (Ai et al., 2019). During processing of positive faces, an increase in anterior insula activation over time was trend-wise associated with time spent with depression in the two-year interval (Opmeer et al., 2016). Finally, cortical thickness of medial orbitofrontal cortex (mOFC) and rostral anterior cingulate cortex (ACC), and hippocampal volume estimates were investigated in relation to burden of the disease between baseline and two-year follow-up, but no changes in brain volume or thickness were related to disease burden (or change in depression severity) (Binnewies et al., 2021). Together these results do not provide firm support for the idea that prolonged depression results in structural and functional 'scars', that could explain the heightened vulnerability associated with recurrent and more enduring depression, though subtle changes may characterize regions associated with integrating emotional and cognitive processes as a function of longer duration of the depressed state.

Antidepressant response: About one-third of the included sample

used anti-depressant medication in the form of SSRI's, which was the only allowed type of medication. While modest, this proportion is likely representative of the outpatient sample in the Netherlands. This allowed us to explore whether medication affected the observations by either omitting the SSRI-users in a sensitivity analysis, or adding SSRI-use (yes/no) as a dummy variable to the within-patient analysis. Excluding SSRI-users or controlling for it statistically had no major effect on the results (van Tol et al., 2010, 2011, 2012; Demenescu et al., 2013). Because we did not specifically investigate effects of SSRI use, by comparing SSRI-using patients with non-using patients, we could not report on regional brain activation or morphometry that is related to antidepressant medication use.

Nevertheless, in an exploratory analysis, it was investigated whether functional connectivity patterns during resting state were predictive of antidepressant non-response as a proxy for treatment-resistance (Geugies et al., 2019). MDD patients from the NESDA Neuroimaging sample that were prescribed at least two types of antidepressant medication (n = 17) were compared to MDD patients that kept the same type of medication (n = 32) and carefully matched healthy controls (n = 19). Using an independent component analysis, lower connectivity of the insula with the salience network was observed in 'treatment resistant' patients compared to the 'responders', and follow-up explorations indicated this was related to switching from a task-positive to a task-negative network mode. This might suggest that insula connectivity could potentially serve as a marker of treatment non-response.

3.3. Symptom related associations

Anxiety Distress Specifier: Over the course of the NESDA study, novel ways of accounting for anxiety symptoms were being proposed to characterize the clinical heterogeneity of MDD. The DSM-5 introduced anxious distress as a specifier to recognize the clinical significance of anxiety for depressed patients, as anxious distress was found to be associated with poorer functioning and outcome (Zimmerman et al., 2019). In the NESDA cohort, it was shown that amygdala responses towards emotional faces were higher in MDD patients who presented with anxious distress (ADS) than in MDD patients without ADS and healthy controls (Nawijn et al., in preparation), but no differences in amygdala-seeded functional connectivity during rest were associated with ADS presence. Furthermore, presence of ADS was associated with lower integrity of the white matter of the anterior thalamic radiation, which was observed independent of presence of a comorbid anxiety disorder, as observed in the 9-year follow-up DTI data (Heij et al., 2019). Also, severity of anxiety distress was negatively related to white matter integrity of the uncinate fasciculus and cingulum pathways. Involvement of these frontolimbic white matter tracts may underpin the maladaptive emotional functioning associated specifically with anxiety symptomatology.

Social dysfunction: MDD is frequently associated with impaired social function, which may persist even after full remission of depressive symptoms. Social dysfunction may hamper occupational and social reintegration, thereby adversely affecting overall prognosis, but its neural substrate is poorly understood. Saris et al. (2020) studied associations between social dysfunction and default mode network connectivity in 74 MDD patients, showing that social dysfunction was linked to diminished default mode network connectivity, in particular within the prefrontal cortex. Whereas the authors considered this finding to be preliminary, it nevertheless may serve as a starting point for more extensive (e.g., multimodal) investigations of the role of the default mode network in social dysfunction (Saris et al., 2020).

Suicidality: Suicidal behaviors, including suicidal ideation and attempting suicide, are common in patients with MDD. It has been proposed that suicidal behavior results from a complex cascade, progression through which is moderated by psychological, environmental and neurocognitive factors (Jollant et al., 2011; O'Connor and Kirtley, 2018). In patients with MDD, Ai et al. (2018) studied the relation between suicidal ideation and attempts, the strongest predictors of suicidal acts, and the fMRI-correlates of emotional face processing and executive planning to understand the potential moderating role of emotion processing and executive control in the occurrence of suicidal acts. One-hundred-three MDD patients were included in the analyses, of whom 49 reported suicidal behavior (n = 18 reported a history of suicidal attempts; n = 31 reported current suicidal ideation) at the time of the NESDA interview. MDD patients with a history of attempts showed lower activation of the bilateral fusiform face area than ideators and patients without suicidal attempts or ideation, and healthy controls, activation that was positively correlated to amygdala activation. Effects were unconfounded by presence of current ideation, a history of childhood maltreatment, symptom severity, or current SSRI- or psychotherapy use. No activation differences were observed during performance of the executive planning task. The authors conclude that neural mechanisms underpinning emotional face processing might differentiate between current thoughts from past suicidal behavior that might facilitate the occurrence of suicidal acts, while non-emotional cognitive control seems relatively intact in suicidal patients.

Biotypes: Dinga and colleagues (2019) attempted to replicate earlier findings by Drysdale et al (2017) identifying biologically meaningful subtypes of depression based on resting state functional connectivity characteristics. In a sample of 187 patients with MDD and/or anxiety disorders, the relation between resting state functional connectivity and symptoms was investigated and it was tested whether reliable subgroups could be identified. However, no significant relations with symptoms nor any reliable subtype could be distinguished. Therefore it was concluded that the evidence for the existence of distinct depressive subtypes based on resting state functional connectivity data should be treated with caution, in view of methodological caveats in the earlier study.

3.4. Aetiological factors

Although understanding the comorbidity of depression and anxiety and the variable and heterogeneous clinical course of both depression and anxiety disorders were the primary aims of the NESDA Neuroimaging study, the wealth of available data related to clinical, environmental and biological characteristics also made the NESDA Neuroimaging study a favorable point of departure to explore the neurocognitive basis of this heterogeneity. Over the last decade, researchers within NESDA have sought to explore functional and morphological brain correlates of individual symptoms and possible etiological factors, including early life stress, personality, and a family history of psychiatric disorders.

Childhood maltreatment: van Harmelen and coworkers investigated the effects of childhood trauma, in particular childhood emotional maltreatment (CEM) on regional brain morphology and emotion processing. CEM was found to be associated with lower dorsomedial prefrontal cortex volume, even in the absence of physical and/or sexual trauma, and irrespective of psychiatric status (van Harmelen et al., 2010). These findings indicated that sustained inhibition of growth or structural damage can occur after exposure to CEM in an area critically involved in emotion regulation, thus providing an important link in understanding the increased emotional sensitivity in individuals reporting CEM. Similar findings were obtained using functional imaging: CEM was associated with enhanced bilateral responsiveness of the amygdala to emotional faces (van Harmelen et al., 2013) and lower medial prefrontal activation during encoding and recognition of neutral and emotional words (van Harmelen et al., 2014). The authors concluded that CEM may increase vulnerability to developing psychopathology on different processing levels in the brain, including enhanced automatic/lower order emotion processing and blunted medial prefrontal cortex activation during higher order cognitive processing. Of note, these CEM-related variations in brain volume and responsivity were also observed in the healthy control participants,

suggesting a stress-exposure related characteristic that does not suffice to explain the development of affective psycho-pathology when counteracted by "resilience-promoting" mechanisms. Also in the NESDA sample, van der Werff et al. (2013) showed that CEM was associated with decreased resting-state functional connectivity (RSFC) between the right amygdala and bilateral precuneus and left insula, as well as with decreased RSFC between dorsal ACC and precuneus. The authors concluded that CEM may profoundly alter RSFC in regions associated with episodic memory encoding and retrieval as well as self-referential processing, which may increase the likelihood for developing affective disorders.

Personality factors: Neuroticism is a personality factor associated with the vulnerability for experiencing negative affect and a known risk factor for developing affective disorders. Therefore, its structural and functional associations have been studied in the NESDA healthy control participants to understand vulnerability factors that might contribute to the development of affective disorders. During viewing of emotional faces, neuroticism was found to positively correlate with right amygdala-dorsomedial prefrontal cortex coupling and negatively with left amygdala-ACC coupling, associated with self-referential processing and top-down control, respectively (Cremers et al., 2010). Neuroticism was also associated with higher amygdala-precuneus resting-state functional connectivity in 50 healthy control participants, again suggesting a link with self-referential processing (Aghajani et al., 2014). On the 'protective' side of the personality spectrum, extraversion, but not neuroticism, was found to be positively correlated with amygdala and orbitofrontal gray matter volume in 65 healthy control participants, which was interpreted as reflecting variable sensitivity to positive, pleasant information (Cremers et al., 2011). This might modulate the extent to which an individual is guarded against stress in the face of negative events. Of note, ACC volume was positively correlated to extraversion in males but not in females, suggesting that the ACC in males is included in the same extraversion mediating regulatory network, thereby providing stronger protective effects against mood disorders (Cremers 2012). Of course, structural variations in healthy control participants should not be interpreted as functional abnormalities, but may predispose to network dysfunctions that may have clinical relevance. In NESDA patients, personality factors have not been extensively studied, though extraversion, used as an inverse proxy of (lack of) negative affect, was found to modulate MDD-related functional connectivity of the ventral striatum, medial prefrontal cortex, and ventrolateral prefrontal cortex, during encoding of emotional words (van Tol et al., 2013). Neuroticism had no effect on depression related task-related functional connectivity in this analysis (van Tol et al., 2013).

Together these results suggest that a vulnerability for negative affect, as indicated by higher levels of neuroticism, relates to functional coupling of primary emotional processing areas with regulatory areas in self-related processing. Extraversion, on the other hand, may modulate both the volume and functional connectivity of areas implicated in reward processing and regulatory control, which may contribute to a higher likelihood of experiencing an enduring negative mood when faced with stressful events.

Cognitive vulnerability: It has been proposed that an imbalance in activation of frontal and limbic structures during processing of negative affective cues underpins the vulnerability for the persistence of negative thinking about oneself, the world, or the future, characteristic of a depression (Disner et al., 2011). Groenewold et al. (2015) investigated in 112 NESDA participants whether the relation between cognitive vulnerability and a fronto-limbic imbalance during processing of negative emotional faces differed between healthy control participants and unmedicated patients with a diagnosis of MDD and/or an anxiety disorder, or was moderated by recent life stress as measured with the list of threatening events (Brugha et al., 1985). Cognitive vulnerability estimates were derived from a set of measures assessing cognitive reactivity, negative attribution styles, and explicit negative self-associations. It was observed that cognitive vulnerability was associated with increased activation of the superior parietal cortex extending to the precuneus during negative vs. positive emotional faces, which was found to be specific for the healthy control participants. No specific associations were observed for the experience of recent life stress. Contrary to expectations, no relation between cognitive vulnerability and amygdala activation during processing of negative stimuli was observed. The authors concluded that these associations may reflect increased efforts needed to ignore irrelevant negative emotional information. Given that the association was only observed in the control participants, increased parietal activation related to increased cognitive vulnerability may suggest compensatory cognitive control in order to maintain a healthy status. The lack of such an association in patients may point to a failed engagement of such compensatory mechanisms.

Family history of alcohol use disorders: A family history of alcohol dependence enhances susceptibility for mood and anxiety disorders and the neurocognitive basis for this predisposition has been studied within NESDA on both functional and structural levels. Sjoerds et al. (2013) demonstrated slower performance and increased dorsal prefrontal activation during planning, and altered insula activation when processing positive emotional words in MDD patients with a family history of alcohol dependence compared to those without, suggesting that the presence of family history contributes to the neurophysiological risk profile of mood/anxiety disorders via affecting cognitive control and processing of positive material. Furthermore, it was observed that MDD patients with a positive family history of alcohol dependence showed lower volume of the right parahippocampal gyrus, also when controlled for severity of current symptomatology, childhood emotional maltreatment and a family history of depression and/or anxiety disorders (Sjoerds et al., 2013). Similar results have been observed in drinking and non-drinking adolescents with a family history of alcohol dependence (Benegal et al., 2007; De Bellis et al., 2005). Therefore, the findings of Sjoerds et al (2013) suggest that abnormal parahippocampal volume represents a biologically persistent vulnerability for alcohol use disorders, and is not the result of neurotoxic effects of alcohol or delayed brain maturation.

3.5. *Biological characteristics: stress, genetic variation and immunometabolic dysregulation*

The combination of extensive biological as well as phenomenological data has allowed the NESDA Neuroimaging project to explore brain correlates of several biological factors and processes postulated to be involved in the pathophysiology of depression, in particular of a number of genes, but also of immunometabolic factors and oxidative stress. More recently, the NESDA MRI longitudinal data has also been used to study the concept of increased brain aging in affective disorders, results which will be published soon.

4. GWAS approach: role of the PCLO gene

PCLO: In 2009, involvement of the presynaptic protein piccolo in the psychopathology of MDD was suggested and confirmed in a genome wide association study (GWAS; Bochdanovits et al., 2009; Sullivan et al., 2009) based on amongst others samples from the NESDA study and the Netherlands Twin register. This GWAS implicated the polymorphism rs2522833 in the piccolo (*PCLO*) gene—involved in monoaminergic neurotransmission—as a risk factor for MDD. Subsequently, the relation of this single nucleotide polymorphism with brain functioning during emotional and cognitive processing was studied (Woudstra et al., 2012). In a sample of 118 patients with MDD and 41 healthy controls, the *PCLO* risk allele was found to be specifically associated with altered emotional face processing, but not with executive dysfunction (Woudstra et al., 2012). In *PCLO* risk allele carriers, increased left amygdala during processing of angry and sad faces was observed compared to non-carriers, independent of psychopathological status. During

processing of fearful faces, the *PCLO* risk allele was associated with increased amygdala activation in MDD patients only. It was suggested that this may represent a link between genotype and susceptibility for depression via altered processing of fearful stimuli.

Also, Woudstra et al (2013) explored the effects of the PCLO risk allele on emotional word encoding and retrieval in 89 MDD patients and 29 controls. They observed lower activation of the insula during negative word encoding in PCLO risk-allele carriers, independent of diagnostic status. In addition, depressed risk-allele carriers showed lower dorsal striatal activation during negative word encoding than non-risk carriers, an effect that was not observed in controls. There was also a blunted amygdala response during identifying new positive words among known positive words in healthy risk allele carriers and all MDD patients. No differential effects during recognition of neutral or negative words were observed. In line with the study on face processing, it was suggested that the *PCLO* risk allele may increase vulnerability for MDD by modulating brain functioning with regard to responsiveness to salient stimuli and their processing. In addition, depression-specific effects of PCLO, i.e. altered dorsal striatal activation during negative word encoding and blunted amygdalar responsivity to novel positive information led the authors to suggest a potential role of PCLO in symptom maintenance in MDD.

5. Candidate gene approach: BDNF, COMT, NPY, and DISC-1

In addition to informing our analyses by the GWAS results, we studied the effects of a number of candidate genetic polymorphisms putatively involved in affective disorders. These included the val66met polymorphism on the BDNF gene, the val158met polymorphism on the gene coding for COMT, the Ser704Cys polymorphism on the Disrupted-in-Schizophrenia -1 (DISC-1) gene, and the NPY-gene.

BDNF: Molendijk et al (2012) used structural and functional MRI data to examine the effect of the BDNF val66met polymorphism on hippocampal volume and encoding related activity of emotional words in 126 patients with affective disorders and 31 healthy controls. Importantly, the NESDA data allowed them to take factors such as childhood emotional maltreatment and psychiatric status into account. They found, controlled for psychiatric status and childhood maltreatment, smaller hippocampal volume in carriers of the met allele. For the encoding task the picture was somewhat different. Controlled for psychiatric status, carriers of the met allele showed increased activation during encoding of negative words compared to non-carriers, but only in those participants without childhood abuse. The authors speculated that the higher levels of encoding activity after exposure to childhood abuse in the non-carriers may reflect a gene-environment interaction.

COMT: The val158met polymorphism of the COMT gene causes altered activity of the COMT enzyme. The COMT enzyme is responsible for the breakdown of catecholamines, including dopamine and norepinephrine, and can be mainly found in the prefrontal cortex and temporal areas. Alternations in catecholaminergic neurotransmission may contribute to disturbed emotional and cognitive processing, probably via altered cortico-subcortical interactions, and may be involved in MDD. The val158met COMT polymorphism was found to be associated with abnormal prefrontal cortex activation during both emotional processing and working memory in healthy controls (see Opmeer et al. (2013) for an overview of studies). Because a direct association between the val158met COMT polymorphism and MDD had never been established, Opmeer et al. (2013) examined this using prefrontal and amygdala activation during an executive planning task and an emotional face processing task as an endophenotype. They included 97 MDD patients and 28 healthy control participants with complete Tower of London executive planning task and face processing fMRI data. An interaction between number of met-alleles and presence of MDD diagnosis was found in the ventrolateral prefrontal cortex during negative emotion processing, with higher activation in risk-(met)-allele carriers in healthy controls. In MDD patients, no relation to the number of risk-alleles was found, but all patients were found to show somewhat higher responsivity of this part of the ventrolateral prefrontal cortex. During the executive planning task, met-alleles were associated with increased dorsolateral prefrontal gyrus activation, but with no modulatory effect of MDD diagnosis. There were no behavioral effects on the two tasks. Together, it was suggested that the COMT risk-allele contributes to compensatory recruitment of lateral prefrontal brain areas during both emotional processing and executive control, but that during emotional processing this was potentially obscured in MDD patients due to the effect of the current depressive state.

NPY: Building on work demonstrating the impact of childhood emotional maltreatment (CEM) on the stress-response system and on brain structure and reactivity, in particular increased amygdala responsiveness, Opmeer et al. (2014) investigated the effects of the c/c/ genotype of neuropeptide Y (NPY) in 85 unmedicated NESDA-patients and 33 healthy controls. NPY has been shown to play an important role in adequate stress-responses and is abundantly expressed in several brain regions, in particular in the amygdala. Previous work found an increased vulnerability for developing psychopathology after CEM in subjects with the C/C genotype. The aim of the study by Opmeer et al., in which baseline data from the implicit emotional face processing task was used, was to investigate whether NPY genotype influenced activity of brain areas involved in emotion processing and whether CEM and presence of affective psychopathology could influence the effect of NPY genotype on the amygdala. It was hypothesized that the combined effect of carrying the risk genotype (i.e. C/C-carriers) and a history of CEM would be associated with the highest amygdala activation. Results only showed interactions between genotype and CEM, irrespective or type of facial emotion displayed. Higher amygdala activation across emotional expressions and less activation of the posterior cingulate cortex, as well as faster behavioral responses, was observed in individuals with CEM and the risk genotype. This effect was consistent with the notion that the combination of risk genotype and CEM may cause hypervigilance, potentially contributing to the increased vulnerability for developing affective disorders after CEM in the carriers of the risk allele.

DISC-1: Finally, the last candidate gene for (vulnerability for) affective disorders examined within the NESDA MRI project was the Disrupted-In-Schizophrenia-1(DISC1) gene (Opmeer et al., 2015). Previous studies found associations suggesting that the DISC1-genotype Ser704Cys (with the Cys-allele as risk-allele) was involved in functioning and structure of hippocampal, ACC and prefrontal regions, regions of major interest for affective disorders. However, no previous study examined associations for the various regions at the same time. Opmeer et al. (2015) therefore studied the effects of Ser704Cys-genotype on function and structure of the ACC, dorsolateral prefrontal cortex, and hippocampus in both patients and controls from NESDA. It was hypothesized that Cys-carriers would show smaller grey matter volumes and less activation in these regions of interest during executive planning and episodic memory. During visuospatial planning, healthy Cys-carriers showed smaller bilateral (para)hippocampal volumes compared with Ser-homozygotes, and lower activation in the ACC and dorsolateral prefrontal cortex (Opmeer et al., 2015). Interestingly, in anxiety patients, these effects were reversed: Cys-carriers showed larger (para)hippocampal volumes and more ACC activation during visuospatial planning. In depressive patients, however, no effect of genotype was observed. The authors concluded that Ser704Cys-genotype influences (para)hippocampal structure and functioning of the dorsal prefrontal cortex during executive planning, but most prominently in unaffected controls, with the presence of anxiety disorders having moderating effects, at least for the aspects examined in this study.

6. Immunometabolic factors and oxidative stress

Immunometabolic dysregulation: Chronic psychological stress has been shown to disrupt the homeostasis of various physiological stress systems, including the immune-inflammatory system and the

hypothalamus-pituitary adrenal (HPA)-axis (see review by Epel (2009)). Prolonged dysregulation of these systems results in systemic low-grade inflammation and metabolic dysregulation. These dysregulations have been associated with the onset and more severe course of multiple psychiatric disorders. Previous work suggested this to be partly due to neuroanatomical changes and impaired neuroplasticity. However, previous neuroimaging studies had not examined multiple markers of immunometabolic dysregulation together, did not correct for lifestyle factors or had modest sample sizes. Since this information was available in NESDA for a fairly large group of patients and controls (n = 283), the effects of multiple markers of immunometabolic dysregulation on the amygdala and ACC, key structures involved in psychological and physiological stress-regulation, were examined by van Velzen et al. (2017a). Interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-a), c-reactive protein (CRP), triglyceride levels and HDL-cholesterol levels were determined in peripheral blood and genomic profile risk scores (GPRS) for immunometabolic dysregulation were calculated. They performed covariate-adjusted linear regression analyses to examine the relationship between immunometabolic dysregulation and brain volume/thickness across included participants. Triglyceride levels and severity of immunometabolic dysregulation were found to be associated with lower rostral ACC thickness across all participants. IL-6 was inversely associated with hippocampal and amygdala volume in healthy controls only. GPRS for immunometabolic dysregulation, however, were not associated with brain volume or cortical thickness. The authors interpreted these findings as showing different serum, but not genetic immunometabolic factors having similar mechanisms of affecting structural properties of the ACC.

Oxidative stress: Oxidative stress is a biological process that may lead to oxidative damage to lipids, proteins, and DNA and ultimately cell death. Studies in rodents showed that brain regions, particularly the amygdala and hippocampus, are sensitive to oxidative stress, but studies on the association between oxidative stress and brain morphology in humans were lacking at the time. In NESDA the association between two robust measures of oxidative damage in plasma (8-OHdG and F2-isoprostanes) and volume of the hippocampus and amygdala was examined in the complete sample of individuals with and without MDD and/or anxiety (N = 297) (van Velzen et al., 2017b). In secondary analyses, van Velzen et al. examined differential effects in patients and controls. 8-OHdG and F2-isoprostanes plasma levels were determined using liquid chromatography tandem mass spectrometry and volume of the hippocampus and amygdala and hippocampal subfields was determined. Authors found no association between plasma markers of oxidative stress and subcortical volume across participants or in the separate patients and control groups. These findings suggest that exposure to oxidative stress is not associated with lower subcortical brain volume and cannot explain the often observed lower volume of the hippocampus in depression (Schmaal et al., 2016).

7. Comment

This paper summarized the research findings from the NESDA Neuroimaging with relevance for understanding the heterogeneity in clinical presentation, course trajectories, and etiology of MDD and common anxiety disorders, that have been published since 2010. Bringing together all these study results brings to light a number of observations. In this section, these observations will be discussed in the light of various neuroanatomical models of depression, including the models of Mayberg (1997) and Phillips et al. (2003) on which the NESDA study was based, but also newer models resulting from meta-analytic findings of the numerous neuroimaging studies published since the '90s.

8. Common characteristics, but no additive effects of depression and anxiety disorder

In NESDA, it was shown for the first time that individuals diagnosed with MDD, a common anxiety disorder (SAD, PD, and/or GAD), or with both MDD and a common anxiety disorder, are characterized by lower volume of the pregenual cingulate cortex, a region critical for integration of emotional and cognitive processing (van Tol et al., 2010). Also, lower volume of the posterior cingulate cortex was observed across diagnostic groups, though at the time of analysis this region was not included as *a priori region* of interest and therefore this result was not emphasized. Additionally, it was observed that hippocampal hypo-activation during the encoding of positive words was characteristic of both MDD and anxiety disorders, or the comorbid condition (van Tol et al., 2012).

However, comorbid depression and anxiety was not associated with more pronounced abnormalities in brain regions associated with emotion processing and cognitive control. Given that comorbidity is often characterized by early onset of either disorders, longer and more burdensome episodes, poorer treatment response and a less favorable clinical course (ter Meulen et al., 2021), it was expected that this clinical severity would be reflected by greater or more extended neurocognitive alterations. However, abnormalities in the comorbid group were often shared with either the patients diagnosed with only MDD or a common anxiety disorder, or both. Examples are the elevated dorsolateral prefrontal cortex and insula responsiveness during executive planning (van Tol et al., 2011) and encoding of negative words (van Tol et al., 2012), respectively, which were found in MDD with and without comorbid anxiety. The only finding that was specific to the comorbid group of patients diagnosed with both MDD and one or more anxiety disorders, was made during a task-free period, where the intrinsic connectivity between networks commonly associated with affective-, self-referential- and cognitive processing were studied (Pannekoek et al., 2015). It was observed that a limbic network showed increased connectivity with regions in self-referential- and executive control networks in patients with both depression and anxiety, unrelated to severity of current symptoms. This suggests that a higher propensity to exchange signals between brain regions involved in networks associated with emotional processing, self-referential processing, and executive control may heighten the vulnerability for enduring affective symptomatology. Increased connectivity between networks may suggest lower network segregation and specialization, that may result in an inefficient network organization. This hypothesis however deserves further testing using a graph theoretical approach that allows testing for network properties.

9. Relevance of 'ventral'/limbic circuitry for depression and anxiety

Notably, no solid support for general increased activation of the amygdala in response to emotional stimuli associated with the presence of a recent diagnosis of MDD or anxiety disorders was provided. This increased activation was predicted from the 'limbic-cortical' emotion processing models of Phillips (2003b) and Mayberg (1997). Nevertheless, other risk factors or current symptom characteristics were associated with abnormal amygdala activity. During emotional face viewing, it was found that higher levels of anxiety symptoms as defined in the anxiety distress specifier, but not comorbid anxiety disorder, were associated with elevated amygdala responsiveness (Nawijn, in prep). Also, type of anxiety disorder appeared to affect amygdala responsivity, and therefore lumping all anxiety disorders might obscure these effects (Demenescu et al., 2013). It was also observed that anxiety severity, independent of anxiety diagnosis, may result in higher amygdala – medial prefrontal cortex connectivity (Demenescu et al., 2013), which suggests that anxiety related symptomatology may moderate both amygdala responsivity and connectivity. Also, presence of childhood maltreatment (van Harmelen et al., 2013), or the PCLO (Woudstra et al., 2012) and NPY risk allele (Opmeer et al., 2014) appears to result in higher amygdala responses to emotional faces, suggesting that higher vulnerability for depression and anxiety may be mediated by increased amygdala responsivity. During encoding of negative emotional words,

higher amygdala response was observed in depressed patients in an acutely depressed state, not in recently remitted patients (van Tol et al., 2012). Independent of anxious comorbidity, higher insula activation during negative word encoding was observed in MDD patients independent of illness severity (van Tol, 2012). No functional and structural 'scarring' related to persistence of the disorder or oxidative stress were observed in the limbic regions (Binnewies, 2021, Ai et al., 2017; Opmeer, van Velzen). This suggests that limbic hyperactivity is involved in the perpetuation of the current episode, rather than in the general vulnerability for the depressive disorder. Nevertheless, neural characteristics during the episode may contain information relevant for the course of the disorder. For example, in the acute phase increased activation of the amygdala during negative processing at baseline, corrected for current illness severity, was found predictive of the depressive course trajectory over the following two years. Amygdala/anterior hippocampal and insula hyperactivation during negative word encoding was found in individuals who failed to remit in the ensuing two years, whereas individuals who would show remission within this period did not show increased responsivity (Ai et al., 2015). Also, using more complex multi-variate prediction methods, face processing data was able to reliably predict disorder status at two-year follow up (Schmaal et al., Frässle). It should be noted here that this result is likely not related to amygdala reactivity only, but was based on whole brain responsivity (Schmaal et al., 2015) or effective connectivity of the amygdala with other regions in face processing (Frässle et al., 2020).

10. Relevance of dorsal/cortical circuitry for depression and anxiety

Using the Tower of London executive planning paradigm, we aimed to test whether abnormal recruitment of the lateral prefrontal cortex, supposedly involved in regulatory control of emotional states, showed abnormalities during non-emotional (visuospatial) task performance. This would inform on the propensity of the frontal cortex to exert regulatory control when needed in the face of stressful or emotional events. We did not find support for a common abnormality across individuals with MDD and anxiety, but showed that slightly elevated dorsolateral prefrontal cortex responsiveness was common to individuals with a diagnosis of MDD, and was most pronounced in acute depressed patients (van Tol et al., 2011). This suggests that lateral prefrontal regions are engaged during solving complex problems that require sustained attention, mental flexibility, and working memory manipulation, and the observed subtle over-recruitment during the acute state may indicate inefficient control mechanisms that may fall short when more stressful conditions are present. This hypothesis could however not be tested because of the non-emotional nature of the task.

During emotional tasks, frontal hypoactivation was not observed in our sample (van Tol et al, 2012; Demenescu 2011). Instead, ventrolateral prefrontal cortex hyperactivation during negative word encoding was observed in acutely depressed patients, irrespective of anxiety comorbidity. This suggests compensatory need for regulatory control when processing negative emotional material. Also, dorsal ACC and dorsolateral prefrontal cortex hyperactivation was observed in the depressed state during processing of positive words and faces, respectively (van Tol et al., 2012; Demenescu et al., 2011). This suggests that increased frontal resources are needed to deal with emotional conflict when content does not match the current mood state. Together with the depression and anxiety common observation of altered hippocampal involvement during positive word encoding, this suggests that altered regulatory control is involved in the perpetuation of the current disorder state.

Additionally, we observed lower volume of the right ventrolateral prefrontal cortex in patients suffering from depression only (van Tol et al., 2010). Given the role of the ventrolateral prefrontal cortex in an emotion regulation circuitry, specifically in signaling the need for regulatory control (Dixon et al., 2017; Kohn et al., 2014), this finding suggests that the propensity to regulate emotions is altered in MDD. Currently we are preparing a manuscript on involvement of prefrontal regions during effortful emotion regulation as a function of nine-year load of depression (van Kleef, in prep) that could shed light on the state vs. trait abnormalities the prefrontal cortical functioning during implicit and effortful regulation of emotions.

Moreover, we did not find support for a role of prefrontal regions in the long-term course of depression, as no associations with persistent depression (Ai et al., 2019; Binnewies et al., 2021; Opmeer et al., 2016), oxidative stress (van Velzen et al., 2017b) or prediction of course was observed (Ai et al., 2015). Nevertheless, medial 'dorsal' prefrontal regions seem to be involved in the general primary vulnerability for developing depression and anxiety disorders, as both structural and functional impairments in the medial prefrontal cortex (van Harmelen et al., 2010, 2014) and resting state connectivity of the dorsal ACC with the default mode network (van der Werff et al., 2013) were associated with the experience of childhood emotional maltreatment, independent of current psychopathological status. See Fig. 2 for an updated ventral-dorsal model of depression, highlighting involvement of components that were supported by structural and functional neuroimaging results from the NESDA Neuroimaging study.

11. Revisiting the limbic-cortical models of depression and anxiety

Paradigms of the NESDA Neuroimaging studies were chosen based on the neuroanatomical models of Mayberg (1997) and Philips et al. (2003a/2003b) in order to test whether these models applied similarly to both depression and anxiety, and whether more pronounced abnormalities in implicated regions could explain comorbidity of depression and anxiety disorders and associated worse clinical profile. The limbic-cortical dysregulation model of Mayberg (1997), informed by studies into secondary depression occurring in neurological disorders, unipolar 'primary' depression, and treatment studies, concerns the general neuroanatomy underpinning sadness in health and depression. In this model, a 'dorsal compartment', including reciprocally connected neocortical and midline limbic structures, is linked to cognitive, attentional and self-initiation disturbances associated with depression. A 'ventral compartment', composed of paralimbic cortical (subgenual ACC), subcortical structures and brainstem regions is associated with vegetative and somatic aspects of the disorder. In this model, the pregenual cingulate cortex has a special position as connector hub responsible for adequate regulatory interaction between ventral and dorsal systems. It is acknowledged that depression is not the result of dysfunction of any of these single brain regions, but of a failure of coordinated interaction between subcomponents of each compartment, or between compartments. Mayberg (1997) recognizes that evidence for consistent involvement of the ventral component is lacking in 'primary' depression, and that large variability in findings could be explained by differences in symptom profiles that need to be studied.

Philips et al. (2003a/b) presented an elegant transdiagnostic two-systems model explaining the occurrence of mood states in health and disease. It used concepts of appraisalist theory to explain how ventral-dorsal contributions and interactions underpin emotion perception, production of affective states, and regulation thereof, and how abnormalities in these two systems could give rise to psychiatric symptoms, including a persistent abnormal mood typical for depression. In short, it suggested that elevated limbic reactivity to emotional material together with lowered involvement of prefrontal regulatory areas, would give rise to a mood that was dominated by the limbic-regions mediated immediate appraisal without being corrected by cognitive reappraisal, mediated by the prefrontal cortex.

Our findings, consistent with many reports following ours (including the voxel-based meta-analysis of Arnone et al., 2016), support the special position of the pregenual ACC in the neuroanatomy underpinning the vulnerability for depression, independent of current symptomatology (also in line with meta-analytic findings of Schmaal et al., 2017;

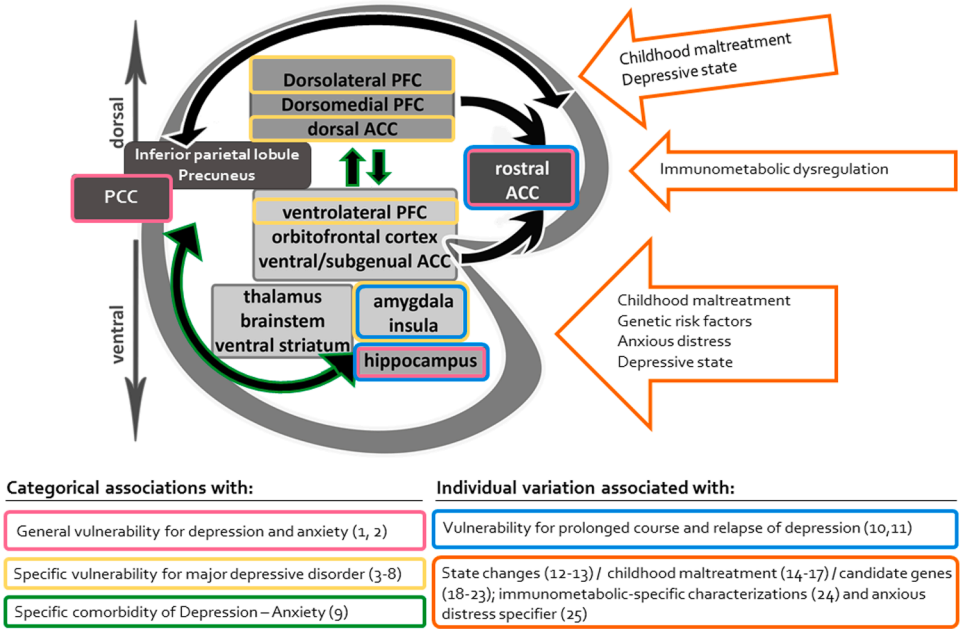

Fig. 2. Summary of NESDA Neuroimaging findings of structural and functional task- and rest-related results, overlaid on an integrated neuroanatomical model including components incorporated in neuroanatomical models of depression (e.g., Mayberg, 1997; Phillips et al., 2003b; Hamilton et al., 2012; Kaiser et al., 2015).
Associations of diagnostic status:
In pink:depression – anxiety common effects: 1) lower pregenual and posterior cingulate cortex volume (van Tol et al., 2010) and 2) lower hippocampus activation during encoding of positive words (van Tol et al., 2012);
In yellow:associations specific for depression: 3) lower ventrolateral prefrontal cortex volume (van Tol et al., 2010); 4) higher ventrolateral prefrontal cortex activation during negative word encoding (van Tol et al., 2012); 5) higher dorsolateral prefrontal cortex activation as a function of increasing planning load (van Tol et al., 2011); 6) increased dorsal ACC activation during encoding of positive emotional words (van Tol et al., 2012) and 7) positive faces (Demenescu et al., 2011); 8) increased insula and amygdala activation during encoding of negative emotional words (van Tol et al., 2012);
In green: effects specific for comorbid depression-anxiety: 9) abnormal limbic-precuneus/posterior cingulate cortex and limbic-lateral prefrontal cortex connectivity during rest (Pannekoek et al., 2015).
Associations of individual variations in course, symptom severity and risk-factors:
In blue: associations with longitudinal course: 10) heightened hippocampus, insula, amygdala activation during negative word encoding was associated with non-remission and longer time to remission (Ai et al., 2015); 11) lower pregenual ACC activation during positive face processing (Opmeer et al., 2016);
In orange: associations with intra-individual changes in depressive state: 12) state-dependent activation in the amygdala and hippocampus during emotional word encoding (Ai et al., 2019) and 13) in the insula, amygdala and dorsolateral prefrontal cortex during positive face viewing (Opmeer et al., 2016); associations with inter-individual difference in the experience of childhood emotional maltreatment: 14) lower volume of the dorso-medial prefrontal cortex (van Harmelen et al., 2010); 15) lower activation of the dorso-medial prefrontal cortex during emotional word encoding (van Harmelen et al., 2014); 16) higher amygdala activation during emotional face viewing (van Harmelen et al., 2013); 17) lower amygdala - precuneus and amygdala – insula/hippocampus connectivity and lower dorsal anterior cingulate cortex – precuneus connectivity during rest (van der Werff et al., 2013); Associations with candidate genes: 18) higher activation amygdala negative faces in PCLO risk-allele carriers (Woudstra 2012); 19) lower insula activation during negative encoding in PCLO risk-allele carriers (Woudstra et al., 2013); 20) lower hippocampal volume in BDNF val66met carriers and higher hippocampus activation during negative word encoding in BDNF val66met carriers, only in individuals who experienced childhood maltreatment; 21) ventrolateral prefrontal cortex activation was associated with number of COMT met-alleles in non-depressed individuals and lower dorsolateral prefrontal cortex activation during executive planning associated with COMT met-alleles (Opmeer et al., 2013); 22) higher amygdala and lower posterior cingulate cortex activation during emotional face processing in NPY risk-allele carriers who experienced childhood maltreatment (Opmeer et al., 2014); 23) lower anterior cingulate and dorsolateral prefrontal cortex activation during planning in healthy DISC-1 risk-gene carriers, no effect inpatients; associations with immunometabolic risk factors: 24) higher dysregulation was associated with lower pregenual ACC thickness (van Velzen et al., 2017a); associationswith anxiety distress: 25) Higher anxiety distress specifier scores related to diminished integrity within the anterior thalamic radiation, uncinate fasciculus and cingulum pathways (Heij et al., 2019). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Goodkind et al., 2015, for parts of the ACC). It also fits the meta-analytic finding of abnormal activation of the pregenual ACC in depression linked to biased emotional processing and cognitive control (Diener et al., 2012). Also, we observed that insular hyperactivation to emotional words was associated with depressive symptomatology independent of depression severity, that was furthermore associated with the longitudinal course (Ai et al., 2015). We did not find additional support for the proposed increased ventral-limbic responsivity and lower lateral prefrontal responsivity to negative emotional stimuli of the Phillips (2003b) model.

Later meta-analytic results of increased limbic responsivity (McTeague et al., 2020; Hamilton et al, 2012), decreased prefrontal control responsivity (Groenewold et al, 2013 for the prefrontal hypo-activation; Hamilton et al., 2012) support the ventral-dorsal model (Philips et al., 2003a/b). However, involvement of the ventral or dorsal component in depression (and anxiety) could not be confirmed by all (Müller et al., 2017; McTeague et al., 2017; Groenewold et al., 2013 for limbic involvement). Variations in anxiety symptomatology, genetic and etiological factors, and course heterogeneity of the disorders observed in our studies, could explain variability in published reports for the ventral compartment. Related to involvement of the hippocampus, abnormal responsivity to positive material (van Tol et al., 2012) does suggest state- and symptomatology independent involvement of this limbic structure, particularly when confronted with mood-incongruent material. This finding does not match the meta-analytic results of Muller et al. (2017) who find no support for memory related abnormalities in depression. However, this discrepancy could relate to the fact that working- and episodic memory tasks were lumped for the Müller meta-analysis, a consideration that was highlighted by Barch and Pagliaccio (2017). Though not observed at the set threshold in our sample (van Tol et al., 2010), lower volume of the hippocampus has been observed consistently in depression (see meta-analysis of Schmaal et al., 2016; Goodkind et al., 2015) and hyperactivation of the amygdala/hippocampus to negative emotional material in anxiety disorders and MDD (McTeague et al., 2020). Recently, multi-modal meta-analytic work provides support for spatial divergence in involvement of the hippocampus and amygdala (and subgenual ACC and putamen) in depression (Gray et al., 2020). Together these results support the involvement of the pregenual ACC, and of 'ventral' hippocampus, amygdala and insula in the psychopathology of depression, whereas no solid support for abnormal reactivity

of medial and lateral prefrontal regions in the context of emotion processing and executive control could be provided. A similar picture emerged from jointly discussing the NESDA neuroimaging reports focusing on a recent diagnosis of MDD (See Fig. 2). Of note, whereas Mayberg (1997) places the hippocampus in the ventral-limbic compartment because of its anatomical connections, Phillips (2003a) labels the hippocampus as part of the dorsal-regulatory component because of its role in effortful regulation of behaviour. This positioning is also based on the role-description provided by Gray and McNaughton (2003), indicating the hippocampus as a general purpose comparator, mainly tasked with resolving goal-conflict in goal-directed behaviour.

12. Updated models of depression

Hamilton and colleagues (2012) refined the limbic-cortical models following an integration of baseline activation- and emotional-task induced responsivity data in a whole-brain voxel-wise meta-analysis. They observed consistent *i*) elevated baseline pulvinar activation and *ii*) increased activation of the amygdala, insula and dorsal ACC and decreased activation in the caudate nucleus and dorsolateral prefrontal cortex in response to negative emotional stimuli. They suggest that the combination of pulvinar activation and limbic reactivity potentiates these parts of the brain's salience circuitry to negative stimuli. Because of earlier reported low striatal dopamine levels associated with depression and the critical role of striatal dopamine in relaying information through the caudate to the dorsolateral prefrontal cortex, they basically suggest that the prefrontal cortex goes uninformed about the need for regulatory control when faced with negative emotional stimuli. This oblivion of the prefrontal cortex then results in the lack of back-projection to the cortical-striatal-pallidal-thalamic circuitry. Though this model elegantly explains the context/valence dependent abnormalities in limbic and cortical response patterns and therefore matches our findings of relative intact prefrontal responsivity during neutral executive planning tasks, our and later meta-analytic findings (Müller et al., 2017; McTeague, 2017) do not solidly support lower caudate and prefrontal reactivity and higher salience-circuitry reactivity to negative emotional stimuli, though subtle hyperactivation of the insula was observed by us (van Tol et al., 2012, which was found to be relevant for the longitudinal course of the depressive disorder (Ai et al., 2015).

At around the same time, Disner et al. (2011) presented their model of depression, integrating the cognitive theory of Aaron Beck (1967) with a review of neuroanatomical and neurophysiological findings. They proposed detailed circuitry models explaining maladaptive cognitive processing involved in generating and maintaining depressive symptomatology, including attentional bias, emotional processing, emotional memory, ruminative tendencies, and dysfunctional attitudes about oneself resulting from the activation of depressive self-referential schemas. Their model in general supports the notion of increased limbic 'bottom-up' reactivity, and attenuated cognitive control over these bottom-up regions, in line with models primarily developed to explain affective dysregulation (e.g. Mayberg, 1997; Phillips et al., 2003b). The Disner model attempts to both explain vulnerability and maintenance of depressive symptomatology, and the occurrence of specific and thus heterogeneous symptomatology, in line with the Research Domain Criteria (NIH) approach. Our paradigms would fit the study of emotional processing, both during the emotional faces and word encoding task, which would support the involvement of higher responsivity of limbic responsivity in the acutely depressed state (van Tol et al., 2012) and long term course of the disorder (ai), though not consistently as no amygdalar abnormalities were observed during face processing (Demenescu et., 2011) but instead elevated dorsolateral prefrontal responsivity when processing mood-incongruent faces (i.e., happy). Overall, recent well-powered meta-analytic findings do not fully support the general idea of heightened bottom-up and decreased top-down processing during emotional processing (Müller et al., 2017, McTeague et al., 2020). Futures studies should investigate how especially the circuitry proposed for maladaptive cognitive functioning is mechanistically involved in ruminative processing and dysfunctional belief underpinning the vulnerability for depressive symptomatology, as proposed by the Disner model (2011).

One component seems to be missing in all discussed models: posterior parietal regions involved in the *default mode network*, a network of posterior and anterior midline and lateral parietal regions (Raichle, 2001) that has gained considerable attention since 2001. It has been linked to self-referential processing, which is highly relevant for internally directed processing modes characteristic of depression and anxiety disorders (See Spreng (2012) for an overview). In the context of depression, it was first mentioned by Greicius et al (2007) who observed that patients with MDD showed elevated functional coupling of the subgenual cingulate cortex and thalamus with the default mode network. The default mode network is also referred to as the task-negative network (Fox et al., 2005), because regions in this network tend to de-activate during execution of an external task, and are activated during rest or self-referential processing. This could explain why these regions are typically not reported when studying task related activation. However, reconceptualizations of the default mode network being critical for goal-directed behavior place the function of this network in a different perspective (Spreng et al., 2014). Nevertheless, numerous resting state functional connectivity focused on depression related intrinsic connectivity differences, though using a variety of methods. We for example did not observe abnormalities in the default mode network in patients with MDD without anxiety using independent component analyses (Veer et al., 2010; Pannekoek et al., 2015), but observed abnormal connectivity between regions of the default mode network with a limbic network in patients suffering from both depression and anxiety (Pannekoek et al., 2015). Kaiser et al (2015) meta-analyzed 25 seed-based resting state fMRI studies, and proposed a neurocognitive network model of depression based on their findings. In this model, it is stated that abnormalities in within-network and between-network connectivity in networks associated with self-referential processing, executive and attentional control, and salience processing may result in perpetuation of current depressive episodes. Specifically, the model describes dysfunctions in multiple networks that may predispose to ruminative thinking: 1) lower functional connectivity among fronto-parietal regions, which may underlie abnormalities in cognitive control, 2) higher functional connectivity between regions in the default mode network, associated with self-referential processing and the frontoparietal network, and 3) lower functional connectivity between the frontoparietal network and a dorsal attentional network, which may bias towards ruminative thoughts at the cost of attending to the outside world. Next, lower functional connectivity in a limbic affective network with midline prefrontal cortical may underpin impairments in regulating emotional states. Finally, abnormal functional connectivity in a ventral attentional network with posterior regions may underpin abnormal salience processing, in particular enhanced processing of predominantly negative emotional material.

In light of recent task-related meta-analysis of cognitive and emotional tasks (Müller et al., 2017; McTeague et al., 2017, 2020), this would suggest that the extent to which depressed individuals engage the prefrontal cortex when instructed to, is unaffected, but that the altered intrinsic connectivity of frontal and parietal regions at rest predisposes to lower engagement when confronted with emotional stimuli. Next, together with higher connectivity to default mode regions, this may result in a bias towards self-related ruminative thoughts, while less attention is paid to the outside world and thus corrective (positive) events may be missed. However, higher regulatory control is needed in the face of salient, negative internal or external stimuli. These salient stimuli are processed to a higher extent, both because of higher responsivity of limbic regions to emotional material (McTeague et al., 2020) and because of lower intrinsic connectivity between limbic regions and medial prefrontal regions (Kaiser et al., 2015), thereby

diminishing automatic regulation. This would suggest that strengthening the intrinsic connectivity between frontal and parietal regulatory areas is key when treating depression, thereby lowering the self-referential processing bias, and also between lateral prefrontal and midline prefrontal areas in order to strengthen emotion regulation capacity, while lowering the responsivity of limbic regions associated with threat and salience detection in order to lower the need for regulatory control.

The brain regions involved in the network-hypothesis and their supposed functionality as proposed by Kaiser et al. (2015), are highly relevant for understanding inadequate emotion regulation that is generally associated with affective disorders and is a target of many effective psychological interventions. Adequate emotion regulation depends on functioning of lateral prefrontal, medial frontal and limbic brain areas (Buhle et al., 2014). Meta-analytic results indeed support that abnormalities in a distributed network of midline parietal and cingulate areas, the insula, lateral prefrontal regions, the putamen, cerebellum and precentral gyrus during emotion regulation are associated with depression and anxiety disorders (Picé-Pérez et al., 2017). Abnormal activation of limbic regions other than the insula was not observed in this meta-analysis, which does not fully support the network model of Kaiser et al. (2015) and ventral-dorsal models, which would suggest abnormalities in both frontal and limbic structures. In the NESDA study, an emotion regulation task was included in the nine-year follow-up MRI-measurement, results of which have not yet been published. This will allow us to study whether neural underpinnings of emotion regulation are associated with the long-term course of depression, but also the task-related connectivity of brain regions in multiple brain networks and thus how the resting-state Kaiser et al model holds for the automatic and instructed regulation of mood states.

Future models of depression need to take into account morphological features, baseline activity and connectivity characteristics, to fully understand the off-set from where stimulus-related activation and connectivity changes emerge. Finally, recent explorations of the time-varying nature of network organization, as also explored NESDA by Geugies et al. (2019), make it evident that also the dynamic nature of the network reconfiguration is an important aspect of understanding both the depressive state related abnormalities involved in perpetuation of the current disorder, as well as the time-varying dynamics on the clinical level including recovery, relapse in newer episodes, and development of comorbid disorders.

12.1. General comments

Even though many neuroimaging studies focused on depression followed the original NESDA neuroimaging studies, the observations are still relevant. Not only have findings been replicated and have original data been fed into larger meta-analytic endeavors (Arnone et al., 2016; Schmaal et al., 2016; 2017), there are still only a limited number of studies out there that studied depression and anxiety disorders in common, and were able to specifically control for the comorbidity. Also, due to the careful clinical longitudinal characterization, the relevance of cross-sectional findings of illness severity for understanding state vs. trait abnormalities could be tested using the longitudinal neuroimaging data (Opmeer et al., 2016; Ai et al., 2019; Binnewies et al., 2021). However, the set-up of the NESDA Neuroimaging study predates the Research Domain Criteria approach and focused on the explanatory power of diagnostic labels rather than symptom dimensions across diagnostic labels. Nevertheless, because of the detailed clinical phenotyping, we were also able to take a dimensional approach (i.e. anxious distress) or symptom focused approach (suicidality). However, these all concern secondary analyses.

Overall, at the start of the NESDA Neuroimaging study, it was expected that we would observe massive effects and large blobs of brain activation or morphology differences given the projected sample sizes. We quickly learned that though the main effects of task were indeed very robust, effects of clinical variations were far more subtle, reflecting a trend in the recent neuroimaging literature. Even in the huge meta-analyses that were performed in the context of the ENIGMA MDD-project in thousands of individuals, it became apparent that solely the label of MDD does not explain a lot of variance, although stable associations have been observed (e.g. Schmaal et al., 2020, 2017, 2016).

Similar conclusions can be drawn from the candidate-gene genetic-neuroimaging approach, chosen by NESDA researchers. We report on significant but small effects of several single nucleotide polymorphisms on the BDNF-, NPY-, COMT, DIS1C, and PCLO-genes on activation during emotional and cognitive processing. We observed main effects of the risk-genotypes, as well as interaction effects of gene and diagnosis, or gene and early life stress. Many effects were observed in the limbic regions, that also were defined of regions of interest. Although these results contributed to theorizing on mechanisms linking the genes to psychopathology, new insights led to the conclusion that much larger samples are necessary to explore genetic variations, as well as using other genetic approaches such as polygenic risk scores (PGRS), or approaches that take into account genetic interactions or correlations among traits with a shared genetic basis.

Some limitations, that have been mentioned in most NESDA Neuroimaging papers, should be mentioned here. Earlier papers based on the NESDA Neuroimaging sample not always adhered to current rigorous standards for multiple comparison correction when reporting results, which should therefore be interpreted with caution. Also, owing to the use of multiple scanners which underwent various upgrades over time, scanner variability potentially resulted in an underestimation of true effects. However, we always controlled for scanner site, and patients and controls were randomly distributed over scanner sites so that no systematic site x group error could have occurred. Furthermore, the clinical severity of the NESDA Neuroimaging sample overall was modest, though a substantial proportion showed moderate to severe symptom severity. Finally, it should be mentioned that the NESDA Neuroimaging data from the baseline measurement was used in many publications, and therefore if any systematic bias occurred in sampling of the population or in the measurements, this bias will have affected many results. Also, many statistical tests have been performed, which would in an experimental set-up require appropriate correction for multiple comparisons. However, various analyses were set-up to explore effects of clinical and etiological variations, that could be considered hypothesis generating in nature and ideally need replication in independent samples. This specifically holds for the candidate-gene approach papers, an approach popular in the first 15 years of the 21th century, but which also often showed low reproducibility. Genome Wide Association studies made evident that a single gene variation is usually unlikely to explain a large part of the complex psychopathology of common mental disorders, making the candidate-gene neuroimaging approach, or exploring gene-behavior associations, in smaller samples rather obsolete. More recent candidate-gene neuroimaging studies typically use larger samples and more sophisticated approaches, with the candidate gene neuroimaging study often being part of a comprehensive set of studies investigating various aspects of the candidate gene such as gene-environment interactions (Gottschalk et al., 2019), intermediate phenotypes and treatment response. Nevertheless, our findings from our neuroimaging genetics studies contributed to advancing this field, and could still provide insight from a neural mechanisms point of view (Meyer-Lindenberg and Weinberger, 2006).

Finally, the NESDA study included paradigms focusing on primary emotional processing and non-emotional cognitive control, but did not include paradigms relevant for reward learning and motivation (Keren et al., 2018). This however is an important aspect of understanding the development and maintenance of depression, as motivational problems are a core component of depression, predictive of an unfavorable course. Recently, the need to frame cognitive dysfunction in the light of goal-directed behavior and motivation and not on its own is elegantly presented by Grahek et al. (2018, 2019), which we recognize as an

important advancement in the field.

12.2. Outlook

Though many papers have been written on the NESDA neuroimaging study, several remaining questions are still being addressed. For example, whether executive planning related neural correlates change upon symptomatic remission or are predictive of the longitudinal course. Also, currently we are investigating the effects of depressive persistence and burden over a nine-year period on white matter integrity, resting state functional connectivity, and correlates of effortful emotion regulation. Results of these analyses are expected in the coming year. Because the number of longitudinal studies related to white matter integrity and resting state connectivity in MDD is limited, we are currently performing the fourth MRI-measurement in which we will attempt to invite all individuals that participated in the nine-year follow-up measurement. During this measurement, T1-weighted structural imaging, DTI acquisition and a BOLD-fMRI acquisition during the resting state will be performed that allow for the characterization of changes in intrinsic functional and structural connectivity and morphology over a 15 year period, when many of the NESDA participants will have also reached ages over 65. This will allow exploring the hypothesis whether affective disorders and associated biological dysregulation results in accelerated aging of the brain in a longitudinal manner, and to explore whether for example persistent psychological rigidity is associated with progressive rigidity of functional brain connectivity.

Availability of NESDA Neuroimaging data

The NESDA Neuroimaging project welcomes requests for collaborations on data-analysis, either as a stand-alone project, or by including NESDA Neuroimaging data in a larger analyses, for example for independent replication. Please contact the authors for further information.

Author statement

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Declaration of Competing Interest

None.

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Supplementary materials

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