**Introduction**

Organisms survive, develop, and prosper by properly approaching rewards and avoiding potential harm/punishments (Higgins, 1997). To achieve these goals, a sufficient level of motivation for goal-directed actions is necessary (Elliot, 2006). Disrupted reward/loss processing constitutes a vulnerability and a maintenance factor for motivation-related symptoms (e.g., anhedonia and apathy) that are pervasive across various diagnostic categories (Bressan & Crippa, 2005; Husain & Roiser, 2018; B. Zhang, et al., 2016). For instance, patients with major depressive disorder (MDD) exhibit a diminished motivation to seek for rewards and they show no response bias toward rewarding stimuli (Eshel & Roiser, 2010). Similiar symptoms have been associated with other diagnoses such as schizophrenia, bipolar disorder, and substance use disorder, suggesting a cross-diagnostic nature of these motivation-related symptoms (Strauss, Waltz, & Gold, 2014; Volkow, Fowler, & Wang, 2003; Whitton, Treadway, & Pizzagalli, 2015). These impairments in motivation significantly compromise quality of life, produce poor financial outcomes, and increase burdens for caregivers and society. It is thus imperative to increase our knowledge about abnormal motivational processing across neuropsychiatric conditions and underlying neural signatures with a functional construct approach (Zald & Lahey, 2017).

Motivational processing is not a unitary construct but rather consists of multiple facets, such as anticipatory and consummatory dimensions. Anticipation refers to the expectation of (and preparation for) future rewards and punishments, whereas consumption refers to a state of experiencing rewards or punishments and encoding their motivational salience (Berridge, Robinson, & Aldridge, 2009; Tarantola, Kumaran, Dayan, & De Martino, 2017). These two distinct aspects of motivational processing are well captured by the monetary incentive delay (MID) task and its variants (Diekhof, Kaps, Falkai, & Gruber, 2012; Gu, et al., 2019; Oldham, et al., 2018; Wilson, et al., 2018), in which a cue indicating the amount of potential reward or loss is followed by a short delay (anticipation phase), then a target is presented that requires behavioral response; finally, the outcome (consumption phase) is revealed based on participant’s performance (Knutson, Fong, Bennett, Adams, & Hommer, 2001; Knutson, Westdorp, Kaiser, & Hommer, 2000). Combined with brain imaging techniques, the MID paradigm allows for decomposing neural signatures of anticipatory and consummatory aspects of motivation (Knutson, Fong, Bennett, et al., 2001; Lutz & Widmer, 2014). Specifically, the ventral striatum (VS), insula, amygdala, and thalamus are consistently engaged by the anticipation of both reward and loss (Wilson, et al., 2018), indicating that these regions consist of a general brain circuit encoding motivational salience rather than positive incentive value per se (Oldham, et al., 2018). Moreover, the consumption of outcome consistently recruits the VS and ventromedial prefrontal cortex (vmPFC) (Cao, et al., 2019; Diekhof, et al., 2012; Gu, et al., 2019; Knutson & Greer, 2008; Oldham, et al., 2018; Plichta & Scheres, 2014; Wilson, et al., 2018).

The MID task has been extensively employed in a wide range of neuropsychiatric conditions, offering a promising opportunity to uncover potential neural markers of motivation-related deficits that may transcend disorders (Knutson & Heinz, 2015; Ziauddeen & Murray, 2010). In particular, VS hypoactivation during the MID anticipation phase is evident across multiple neuropsychiatric disorders, including schizophrenia (Grimm, et al., 2014), mood disorders (Knutson, Bhanji, Cooney, Atlas, & Gotlib, 2008), social anxiety (Maresh, Allen, & Coan, 2014), attention deficit hyperactivity disorder (Ströhle, et al., 2008), and alcohol use disorder (Beck, et al., 2009). Blunted VS activation is associated with self-reported anhedonia, reductions in anticipatory pleasure, and severity of depressive symptoms (Arrondo, et al., 2015; Juckel, et al., 2006; Schlagenhauf, et al., 2008; Stoy, et al., 2012; Stringaris, et al., 2015). Conversely, many studies have revealed comparable striatal responses to the consummatory phase between psychiatric patients and healthy controls (e.g., Bjork, Smith, Chen, & Hommer, 2012; Figee, et al., 2011; Hanssen, et al., 2015; Murray, Shaw, Forbes, & Hyde, 2017; Ubl, et al., 2015; Wotruba, et al., 2014). Together, advances in experimental paradigms and brain imaging techniques have provided a more nuanced understanding of dysfunctional motivation processing in neuropsychiatric conditions.

With an increasing body of evidence showing the dysfunctional motivation processing in different disorders, motivation processing deficits have been frequently proposed to constitute a fundamental domain that cut across traditional diagnoses (e.g., Bjork, Knutson, & Hommer, 2008; Cuthbert, 2014a; Cuthbert & Insel, 2013). This transdiagnostic view of the motivational dysfunctions is well in line with a hierarchical model of psychopathology, holding that psychopathological symptoms consist of four levels in an ordered structure: individual symptoms, first-order dimensions (resembling traditional diagnoses), broader second-order factors (e.g., internalizing vs. externalizing) and a general psychopathology factor (i.e., the p-factor) (Lahey, Krueger, Rathouz, Waldman, & Zald, 2017; Zald & Lahey, 2017). In light of this framework, common motivational processing deficits might represent neuropsychological markers of higher-order dimensions that cut across specific diagnoses (Husain & Roiser, 2018; Knutson & Heinz, 2015). Nevertheless, this proposal is mainly based on narrative reviews, focuses on the reward-related (but not loss-related) processing, and largely ignores the heterogeneity of findings in the literature. Therefore, a meta-analytic study is needed to quantitatively synthesize common neural circuit disruptions in motivation (i.e., both reward and loss) processing across diagnoses, while overcoming the heterogeneity and divergence of previous results from limited-size samples (Fox, 2018; Gurevitch, Koricheva, Nakagawa, & Stewart, 2018).

Recent meta-analytic studies on MID have examined the neural circuits commonly engaged by anticipatory and consummatory aspects of motivation in healthy populations (Dugre, Dumais, Bitar, & Potvin, 2018; Gu, et al., 2019; Oldham, et al., 2018; Wilson, et al., 2018). However, to date, there has been no meta-analytic evidence on the common neural signatures underlying motivational processing in different clinical/at-risk conditions, and more importantly, on the common brain function disruptions in anticipatory motivation processing. Beyond the MID task, recent meta-analytic studies have examined reward-processing deficits in specific clinical populations, such as mood disorders (Halahakoon, et al., 2020; Keren, et al., 2018; W. N. Zhang, Chang, Guo, Zhang, & Wang, 2013) and schizophrenia spectrum disorders (Radua, et al., 2015). These case-control meta-analyses provide important insights into the aberrant neural reward processing for specific diagnoses, but they cannot uncover the common neural circuit responsible for abnormal motivation processing across disorders. In other words, the widely-used case-control approach reflects the endeavor to map neurobehavioral markers to the first-order dimensions of psychopathology, but it ignores the shared variance among first-level dimensions and thus impedes investigations of transdiagnostic mechanisms of psychopathology (T. Li, et al., 2020; Zald & Lahey, 2017).

A transdiagnostic meta-analysis of psychiatric neuroimaging studies is well-suited to address this issue by synthesizing neural underpinnings nonspecifically associated with multiple forms of psychopathology. That is, the transdiagnostic approach aims at the shared variance among first-level dimensions and thus investigates higher-order dimensions of psychopathology (see also Zald & Lahey, 2017). Notably, more and more evidence has indicated that mappings between psychopathology and neurobehavioral systems might be more robust at the higher-order factors rather than at lower first-order dimensions (Kaczkurkin, et al., 2018; Kaczkurkin, et al., 2019; Katharina, et al., 2018; Neumann, et al., 2020; Romer, et al., 2018; Shanmugan, et al., 2016; Snyder, Hankin, Sandman, Head, & Davis, 2017; Weissman, et al., 2019). For instance, a wide array of psychiatric disorders broadly share a large portion of their common genetic variation (Brainstorm, et al., 2018), suggesting that higher-order factors account for a larger proportion of heritable variance than first-order dimensions (Lahey, Van Hulle, Singh, Waldman, & Rathouz, 2011). These findings highlight the importance of identifying neurobiological systems linked to overarching dimensions of psychopathology that cut across diagnoses. Therefore, we conducted a meta-analysis of neuroimaging studies on the MID across categorical diagnoses to search for transdiagnostic brain dysfunctions in motivational processing, leveraging abundant evidence from brain imaging studies of the MID in the past decades as well as the distinctions between reward-related and loss-related processing and between anticipatory and consummatory aspects of motivation in the MID paradigm.

Notably, the current transdiagnostic meta-analysis was complemented with a novel and validated technique termed lesion network mapping (Boes, et al., 2015; Darby, Horn, Cushman, & Fox, 2018; Darby, Joutsa, Burke, & Fox, 2018) to examine potential networks encompassing lesion locations causing motivation-relevant functional deficits (e.g., anhedonia and apathy). This novel approach maps lesion-induced symptoms to brain networks rather than specific regions by combining lesion locations with maps of resting-state functional connectivity (RSFC) derived from normal nonsymptomatic populations (Boes, et al., 2015; Darby, Laganiere, Pascual-Leone, Prasad, & Fox, 2017; Ferguson, et al., 2019). Specifically, the lesion network mapping consists of following steps: (i) the volume of each lesion is reproduced onto a reference brain; (ii) the network of brain areas functionally connected to each lesion location are assessed with RSFC; and (iii) the networks associated with each lesion are thresholded and overlaid to determine common network sites across the lesions. Lesion network mapping is well-suited to examine the neurobiological basis of complex symptoms embedded in a distributed brain network consisting of heterogeneous regions (Fox, 2018). In our case, lesion network mapping can provide complementary evidence for the meta-analysis by revealing whether brain networks causally linked to motivational deficits (e.g., anhedonia and apathy) overlap with brain areas ensuing from reward/loss processing deficits across neuropsychiatric conditions. Despite of recent narrative reviews linking different lesion locations to motivational impairments (e.g., Husain & Roiser, 2018; Le Heron, Holroyd, Salamone, & Husain, 2019), to our knowledge, no study has so far quantitatively examined convergence across lesion locations causing apathy or anhedonia in terms of their functional connectivity profiles. Such a network approach is particularly relevant to identify neurobiological systems causally linking to motivational functioning as a complex and multidimensional construct. Indeed, it is becoming increasingly acknowledged that human motivation-related processing can be better understood in terms of interactions across large-scale brain networks comprising of distributed brain locations rather than in terms of specific structures (see also Husain & Roiser, 2018). Together, the current study aimed to identify transdiagnostic neural circuit disruptions in motivational processing across neuropsychiatric conditions and to provide data-driven quantitative inference on the functions of identified nodes from the perspective of system neuroscience with the lesion network mapping approach.

**Materials and Methods**

**Literature search and selection**

Asystematic online database search was performed in accordance with the PRISMA-guidelines (Shamseer, et al., 2015) and best practice recommendations for neuroimaging meta-analysis (Müller, et al., 2017; Tahmasian, et al., 2019). The search was finished in April 2022 and included the PubMed and ISI Web of Science databases using the combination of relevant search terms (i.e., ["monetary incentive delay" OR "MID task" OR "anticipation of reward" OR "reward anticipation" OR "social incentive delay" OR "SID task" OR "incentive delay task"] AND ["functional magnetic resonance imaging" OR "fMRI" OR "positron emission tomography" OR "PET"]). Moreover, we explored several other sources, including: (i) the BrainMap database (http://brainmap.org); (ii) the bibliography and citation indices of the preselected articles; (iii) the reference list of relevant reviews (Balodis, et al., 2012; Grimm, Kaiser, Plichta, & Tobler, 2017; Haber & Knutson, 2010; Knutson & Cooper, 2005; Knutson & Heinz, 2015; Oldham, et al., 2018; Plichta & Scheres, 2014); and (iv) direct searches of the names of frequently occurring authors. The identified articles were further assessed according to the following criteria. First, subjects performed a MID task or its variants (Knutson, Adams, Fong, & Hommer, 2001; Knutson, Fong, Adams, Varner, & Hommer, 2001). Second, we restricted the meta-analysis to studies that employed the functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) imaging modality. Third, results from whole-brain general-linear-model-based analyses (rather than region of interest [ROI] analyses) were provided, given that ALE approach assumes that each voxel has a priori the same chance of being activated (Müller, et al., 2018). Fourth, each study referred to at least one comparison between a neuropsychiatric/at-risk group versus a control group using functional brain imaging data. Finally, activations were presented in standardized stereotaxic space (Talairach or Montreal Neurological Institute, MNI). Note that for publications reporting Talairach coordinates, a conversion to MNI coordinates was employed with an icbm2tal algorithm (Lancaster, et al., 2007). Filtering the search results according to the inclusion/exclusion criteria yielded a total of 129 published fMRI or PET articles (**Table S1**).

**Main ALE approach**

A coordinate-based meta-analysis of selected neuroimaging studies was conducted, employing the ALE algorithm (in-house MATLAB scripts) (Eickhoff, Laird, Fox, Lancaster, & Fox, 2017; Eickhoff, et al., 2009). The ALE algorithm determines the convergence of foci reported from different functional (e.g., blood-oxygen-level dependent contrast imaging) or structural (e.g., voxel-based morphometry) neuroimaging studies with published foci in either Talairach or MNI space (Laird, et al., 2005; Turkeltaub, Eden, Jones, & Zeffiro, 2002). The ALE algorithm interprets reported foci as spatial probability distributions, whose widths are based on empirical estimates of spatial uncertainty due to between-subject and between-template variability of the neuroimaging data (Eickhoff, et al., 2009). The ALE algorithm weights between-subject variability based on the number of subjects analyzed, modeling larger sample sizes with smaller Gaussian distributions and, thus, presupposing more reliable approximations of the "true" activation observed in larger sample sizes (Eickhoff, et al., 2009).

The union of the individual modulated activation maps, first created from the maximum probability associated with any one focus (always the closest one) for each voxel (Turkeltaub, et al., 2012), was then calculated to obtain an ALE map across studies. This ALE map was assessed against a null-distribution of random spatial associations between studies using a non-linear histogram integration algorithm (Eickhoff, Bzdok, Laird, Kurth, & Fox, 2012; Turkeltaub, et al., 2012). Furthermore, the average non-linear contribution of each experiment for each cluster was calculated from the fraction of the ALE values at the cluster with and without the corresponding experiment (Eickhoff, et al., 2016). Based on the calculated contribution, we employed two additional criteria to select significant clusters: (i) the contributions to one cluster were from at least two experiments to prevent findings from being driven by the results from a single experiment; and (ii) the average contribution of the most dominant experiment (MDE) did not exceed 50%, and the average contribution of the two most dominant experiments (2MDE) did not exceed 80% (Eickhoff, et al., 2016).

Applying the ALE algorithm, the reported coordinates of brain areas associated with reward/loss anticipation or consumption converged across different experiments. Neural signatures of reward/loss processing converged using the following meta-analytic schemes: (i) reward anticipation in healthy controls (101 experiments, 1415 foci, and 2421 subjects) or clinical/at-risk conditions (37 experiments, 371 foci, and 911 subjects); (ii) hypoactivity (40 experiments, 277 foci, and 1748 subjects) or hyperactivity (25 experiments, 191 foci, and 1565 subjects) of reward anticipation in clinical/at-risk conditions compared to healthy controls; (iii) loss anticipation in healthy controls (52 experiments, 514 foci, and 1309 subjects) or clinical/at-risk conditions (26 experiments, 219 foci, and 688 subjects); (iv) hypoactivity (18 experiments, 74 foci, and 697 subjects) of loss anticipation in clinical/at-risk conditions compared to healthy controls; (v) reward consumption in healthy controls (44 experiments, 454 foci, and 1122 subjects) or clinical/at-risk conditions (21 experiments, 210 foci, and 636 subjects); and (vi) hypoactivity (15 experiments, 106 foci, and 504 subjects) or hyperactivity (17 experiments, 209 foci, and 970 subjects) of reward consumption in clinical/at-risk conditions compared to healthy controls. It should be noted that meta-analyses were not conducted for hyperactivity of loss anticipation (11 experiments, 71 foci, and 530 subjects) or contrasts associated with loss outcome (healthy controls: 15 experiments, 101 foci, and 445 subjects; clinical/at-risk conditions: 9 experiments, 47 foci, and 385 subjects; hypoactivity: 4 experiments, 24 foci, and 164 subjects; hyperactivity: 3 experiments, 25 foci, and 160 subjects) due to the limited number of experiments (see also Müller, et al., 2018) (**Table S1-S5**).

All maps were thresholded using a cluster-level family-wise error correction (*P* < 0.05) with a cluster-forming threshold of *P* < 0.001 using 10,000 permutations for correcting multiple comparisons.

**Conjunction analyses**

To further examine the overlaps or correspondence between different processes and conditions, conjunction analyses were implemented for the following pairs of contrasts: (i) reward anticipation among healthy controls and clinical/at-risk conditions; (ii) loss anticipation among healthy controls and clinical/at-risk conditions; (iii) reward consumption among healthy controls and clinical/at-risk conditions; and (iv) hypoactivation in clinical/at-risk conditions relative to the controls for reward and loss anticipation. The conjunction analyses were implemented by identifying the intersection between two corrected ALE results.

**Modulation effects**

For the clusters identified in contrasts involving direct comparisons between healthy controls and clinical/at-risk conditions (i.e., hypoactivation in the reward or loss anticipation and hyperactivation in the reward consumption), per-voxel probabilities were extracted to investigate potential modulating effects of demographic, clinical and imaging-specific factors, including mean age, sex ratio, medication status, neuropsychiatric condition, comorbidity and MRI magnetic field strength (see also Goodkind, et al., 2015; Jenkins, et al., 2016; T. Li, et al., 2020). Nonparametric Kruskal-Wallis H, Wilcoxon Rank Sum Test, and Spearman's rank correlation tests were utilized as warranted. However, it should be noted that we did not assess modulating effects of some potentially influential factors (e.g., IQ, duration of disease) that were not reported in most studies.

**Lesion network analysis**

***Case selection***

Case reports of lesion-induced apathy or anhedonia were identified from PubMed and ISI Web of Science databases using the combination of relevant search terms ("apathy" OR "anhedonia" OR "avolition" OR "abulia" OR "akinetic mutism") AND ("MRI" OR "CT" OR "neuroimaging") AND ("damage" OR "stroke" OR "hemorrhage" OR "tumor" OR "lesion") in April 2022. The search resulted in 618 articles, and the abstract or full text was read from 382 publications which were considered to be relevant according to their titles. These publications were subjected to additional inclusion/exclusion criteria in light of previous studies (Boes, et al., 2015; Darby, et al., 2017; Fasano, Laganiere, Lam, & Fox, 2017; Fisher, Towler, & Eimer, 2016; Joutsa, Horn, Hsu, & Fox, 2018; Laganiere, Boes, & Fox, 2016). The inclusion criteria were: (i) case description of motivation deficits in a patient; (ii) neurological examination documenting apathy or anhedonia symptoms presumed to be caused by an intraparenchymal brain lesion; and (iii) clearly delineated and circumscribed brain lesions displayed to be transcribed onto a standard brain template. The exclusion criteria were: (i) extrinsic compression injuries without a clearly represented intraparenchymal lesion; (ii) poor image resolution such that lesion boundaries could not be delineated; (iii) significant mass effects. Filtering the searched articles according to the above inclusion/exclusion criteria yielded a total of 105 cases from 67 published articles (**Table S18**).

***Lesions***

Lesion locations from original published figures were manually traced onto a standard template brain as described previously (Boes, et al., 2015; Darby, et al., 2017; Fasano, et al., 2017; Fischer, et al., 2016; Joutsa, et al., 2018; Laganiere, et al., 2016). Neuroanatomical landmarks were used to ensure accurate transfer onto the template. Specifically, lesions were mapped by hand onto the MNI152 T1 template with 2 mm isotropic voxels using FSL (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012) to make binary lesion masks (value 1 for voxels included to the lesions and value 0 for other voxels). It should be noted that when utilizing this methodology, it was unrealistic to capture the whole 3D lesion volume but only representative 2D slices. However, earlier works suggest that 2D slices can fill in equitable approximation of 3D lesions for lesion network mapping (Boes, et al., 2015; Darby, et al., 2017). In cases where multiple lesions were displayed, all lesions were mapped together and treated as a single lesion for ensuing analyses (Fasano, et al., 2017; Laganiere, et al., 2016).

***Lesion network mapping***

Lesion network mapping was used to investigate the networks associated with apathy or anhedonia. The analysis steps of this technique has been described in the Introduction (see also Boes, et al., 2015; Corp, et al., 2019; Darby, Horn, et al., 2018; Darby, et al., 2017; Fischer, et al., 2016; Laganiere, et al., 2016).

***Specificity***

To access the specificity of lesion brain mapping results, we implemented two control analyses. First, we conducted the same analysis with 105 random lesions to assure that the results were specific to apathy and/or anhedonia rather than reflecting a collection of similarly sized but randomly distributed lesions. Specifically, ten separate randomized control groups were generated through ten repetition of the lesion randomization process, each with 105 randomized lesions, thus resulting in a total of 1050 randomized lesions. When conducting this randomized method, we controlled for the degree of lesion overlap as well as interlesion distances (see also Boes, et al., 2015; Laganiere, et al., 2016). Second, we adopted lesions causing an assortment of different neurological symptoms from a previous study (Boes, et al., 2015) as control samples, including peduncular hallucinosis, auditory hallucinosis, central post-stroke pain, and subcortical expressive aphasia.

**Results**

**Studies included in meta-analyses**

Our meta-analyses included 129 PET/fMRI studies that recruited healthy controls and/or different clinical/at-risk conditions. In particular, the following clinical/at-risk conditions were included in the current meta-analysis (see also Table 1): (1) addiction-related conditions, including alcohol-dependence, cannabis users, cocaine-dependence, nicotine smokers, and pathological gambling (68 experiments); (2) mood/anxiety-related conditions, including anxiety disorders, bipolar disorder, early life stress, major depressive disorder, obsessive-compulsive disorder, and rumination symptoms (50 experiments); (3) neurodevelopmental conditions, including attention deficit hyperactivity disorder and autism spectrum disorder (37 experiments); (4) psychosis-related conditions, including schizophrenia, subclinical psychotic experiences, and high risk for psychosis (25 experiments); (5) personality-related conditions, including borderline personality, external disorder (mainly oppositional defiant disorder), and high sociodemographic risk for antisocial behaviors (9 experiments); (6) eating disorder conditions, including binge eating disorder and obesity (4 experiments); and (7) other conditions, including body focused repetitive behaviors, Huntington’s disease, and impulsivity traits (6 experiments).

**< Insert Table 1 here >**

**Main ALE meta-analyses**

***Reward anticipation***

In healthy controls, consistent maxima were identified in the bilateral VS (extending to the amygdala, thalamus, and anterior insula [AI]), supplementary motor area (SMA), precentral gyrus, middle occipital gyrus, and right calcarine (**Fig. 1A**). In clinical/at-risk conditions, consistent maxima were found in the bilateral VS, AI and left precentral gyrus (**Fig. 1B**). Examining the contrasts of hypoactivation in clinical/at-risk conditions relative to controls demonstrated consistent maxima in the left VS (**Fig. 1C**). No significant consistent maxima were identified for the contrasts of hyperactivation in clinical/at-risk conditions relative to controls. More details on the contribution of each study in each identified brain region are illustrated in **Table S6-S9**. The main findings described above have been validated using leave-one-experiment-out (LOEO) scheme (see Supplementary Information, **Fig. S1**).

**< Insert Fig. 1 here >**

Moreover, for the left VS identified in the contrasts of hypoactivation in clinical/at-risk conditions relative to controls, modulation analyses revealed no significant modulating effects of clinical, demographic or imaging-specific factors (*P* > .05 for all).

***Loss anticipation***

In healthy controls, consistent maxima were identified in the bilateral VS (extending to the amygdala, thalamus, and AI), SMA and left middle occipital gyrus (**Fig. 2A**). In clinical/at-risk conditions, consistent maxima were found in the bilateral VS, thalamus, SMA, precentral gyrus, and left AI (**Fig. 2B**). Examining the contrasts of hypoactivation in clinical/at-risk conditions relative to controls demonstrated consistent maxima in the left VS, middle occipital gyrus and cuneus (**Fig. 2C**). Details on the contribution of each study in each identified brain region are included in **Table S10-S13**. The main findings described above have been validated using LOEO scheme (see Supplementary Information, **Fig. S2**).

**< Insert Fig. 2 here >**

Moreover, for the left VS, middle occipital gyrus and cuneus identified in the contrasts of hypoactivation in clinical/at-risk conditions relative to controls, modulation analyses revealed no significant modulating effects of clinical, demographic or imaging-specific factors (*P* > .05 for all).

***Reward*** ***consumption***

In healthy controls, consistent maxima were identified in the bilateral VS, vmPFC, and posterior cingulate cortex (**Fig. 3A**). In clinical/at-risk conditions, consistent maxima were found in the bilateral VS and vmPFC (**Fig. 3B**). No significant consistent maxima were identified for the contrasts of hypoactivation in clinical/at-risk conditions relative to healthy controls. Examining the contrasts of hyperactivation in clinical/at-risk conditions relative to controls demonstrated consistent maxima in the left inferior parietal lobule (IPL) (**Fig. 3C**). Details on the contribution of each study in each identified brain region are included in **Table S14-S17**. The main findings described above, except the hyperaction in the IPL, have been validated using LOEO scheme (see Supplementary Information, **Fig. S3**).

**< Insert Fig. 3 here>**

Moreover, for the left IPL identified in the contrasts of hyperactivation in clinical/at-risk conditions relative to controls, modulation analyses revealed a significant effect of sex ratio in the clinical/at-risk conditions (*P* < 0.05, uncorrected), but modulating effects of other clinical, demographic or imaging-specific factors were not significant (*P* > .05 for all).

In summary, our main ALE meta-analyses revealed that anticipations of both reward and loss engage the involvement of the VS, AI, and SMA in both healthy controls and clinical/at-risk conditions. These findings are in line with recent meta-analytic findings in the healthy populations (e.g., Dugre, et al., 2018; Gu, et al., 2019; Oldham, et al., 2018; Wilson, et al., 2018) but further provide novel evidence in the clinical/at-risk conditions. More importantly, our results provided the first meta-analytic evidence on the transdiagnostic hypoactivation of the left VS in response to both reward and loss anticipation. Regarding the reward consumption, our results revealed that reward outcome activates the vmPFC and VS among both healthy controls and clinical/at-risk conditions. Finally, clinical/at-risk conditions (vs. healthy controls) exhibited common hyperactivation of the IPL in response to reward outcome.

**Conjunction findings**

The conjunction analysis revealed common activation maxima in the bilateral VS, AI and left precentral gyrus for reward anticipation among healthy controls and clinical/at-risk conditions (**Fig. 4A**). The conjunction analysis of loss anticipation between healthy controls and clinical/at-risk conditions revealed overlaps in the bilateral VS, SMA, left AI and thalamus (**Fig. 4B**). Overlaps of the above two conjunction analyses were identified in the bilateral VS, left AI and thalamus (**Fig. 4C**). Finally, reward consumption among healthy controls and clinical/at-risk conditions showed overlaps in the bilateral vmPFC and right VS (**Fig. 4D**).

**< Insert Fig. 4 here>**

Regarding the contrasts of hypoactivation in clinical/at-risk conditions relative to controls, reward and loss anticipation showed an overlap in the left VS. That is, clinical/at-risk conditions showed hypoactivation of the left VS compared to healthy controls during the anticipation of both reward and loss (**Fig. 5A**).

In short, our conjunction analyses demonstrated that reward and loss anticipation commonly activate the VS, AI and thalamus across both healthy controls and clinical/at-risk conditions. Moreover, reward outcome activates the vmPFC and VS across healthy controls and clinical/at-risk conditions. Finally, there was a transdiagnostic hypoactivation of the left VS for both reward and loss anticipation.

**Lesions causing apathy or anhedonia**

In our literature search for lesions causing apathy or anhedonia, we identified 105 lesion cases (**Fig. S4**). Lesions were anatomically heterogeneous and comprised of various brain areas. Next, we computed the network associated with each lesion location and identified areas of an overlapping network (**Fig. S5**).

In spite of marked heterogeneity in lesion location, the lesions causing apathy or anhedonia were parts of a common brain substrate. The level of overlap of lesion-derived networks was high (75%) and occurred mainly within the bilateral VS and anterior cingulate cortex (**Fig. 5B**). Notably, the left VS was found in the conjunction between the lesion brain network and brain regions identified within the hypoactivation in clinical/at-risk conditions relative to controls within the reward and loss anticipation conjunction analysis (**Fig. 5C**). In this region of interest (ROI) in the left VS, the connectivity strength was higher for the lesions causing apathy and/or anhedonia compared to those from similarly sized lesions randomized to different locations (*P* < 3.66 × 10-18) or a group of lesions causing irrelevant neurological symptoms (*P* < 0.008). Furthermore, similar results were found for the VS ROI identified with the ALE conjunction analysis (i.e., hypoactivation contrast, reward anticipation ∩ loss anticipation), such that the connectivity strength was higher for the lesions causing apathy or anhedonia compared to those from similarly sized lesions randomized to different locations (*P* < 1.05 × 10-12) or a group of lesions causing irrelevant neurological symptoms (*P* < 0.003).

**< Insert Fig. 5 here>**

In short, our lesion network mapping results indicated that heterogeneous lesions causing loss of motivation are parts of a distributed brain network with the VS as one of its key nodes. Notably, our results demonstrated an overlap in the left VS between the key nodes identified in the lesion network mapping and the meta-analytic findings on the hypoactivation in the reward and loss anticipation. Finally, the identified network overlap was specific compared to randomized lesions and to lesions causing irrelevant neurological symptoms (Boes, et al., 2015). To the best of our knowledge, these findings provide the first empirical evidence showing that the VS subserves a key node in a distributed brain network which encompasses heterogeneous lesion locations causing motivation-related symptoms.

**Discussion**

Motivational dysfunction has been proposed to constitute one of the fundamental dimensions of psychopathology cutting across traditional diagnostic boundaries (e.g., Knutson & Heinz, 2015). The current study examined the hypothesis by exploring the common neurobiological basis of motivation-related deficits across neuropsychiatric conditions, leveraging extensive brain imaging studies employing the MID task among diverse clinical and preclinical samples as well as cumulative cases of lesion-induced motivational symptoms. Consistent with recent frameworks, our meta-analytic results identified transdiagnostic hypoactivation in the VS during the anticipation of both reward and loss. The reliability of meta-analysis findings was further validated by LOEO analysis. Our findings were also robust to the modulation effects of demographic (e.g., mean age, sex ratio), clinical (e.g., clinical diagnoses, comorbidity) or imaging-specific (e.g., MRI magnetic field strength) factors. Second, the lesion network mapping approach revealed that heterogeneous lesions causing loss of motivation are parts of a distributed brain network with the VS as one of its key nodes. Notably, we further demonstrated correspondence in the VS between the results derived from our meta-analysis and those from lesion network mapping. To our knowledge, this study is the first to provide meta-analytic evidence of transdiagnostic alternations in neural anticipatory motivation processing that are causally linked to motivation-related deficits. In other words, motivational dysfunction across neuropsychiatric conditions is rooted in disruptions of a common large-scale brain network anchored in the VS.

The current findings agree with dimensional or hierarchical models of psychopathology advocated in past years (Cuthbert, 2014b; Insel, 2014; Lahey, et al., 2017). For example, the Research Domain Criteria Project (RDoC) claims that mental disorders may reflect dysfunction in a small number of transdiagnostic functional constructs measured at different levels (e.g., brain-imaging measures) (Insel, et al., 2010; Insel & Landis, 2013; Charles A Sanislow, Ferrante, Pacheco, Rudorfer, & Morris, 2019; C. A. Sanislow, et al., 2010; Victor, et al., 2018). In this regard, brain regions revealed in the current transdiagnostic meta-analyses might correspond to the RDoC dimensional functional construct of negative/positive valence, abnormalities of which manifest in disorder-spanning symptoms. Moreover, our findings align with the hierarchical models of psychopathology, such that the shared VS alterations altercations might reflect nonspecific neural correlates of second-order factors (e.g., externalizing or internalizing) or the general psychopathology factor (Zald & Lahey, 2017). Notably, it is likely that the transdiagnostic functional construct or higher-order psychopathology factors are embedded in large-scale network disruptions, rather than localized dysfunctions in individual nodes (Buckholtz & Meyer-Lindenberg, 2012; Sha, Wager, Mechelli, & He, 2019; Zald & Lahey, 2017). This conjecture is supported by our lesion network mapping showing that the VS represents a key node in a large-scale network consisting of multiple heterogeneous brain regions, the lesions to which cause motivational impairments. In short, our findings indicate that dysfunctions in the VS-related network represent a transdiagnostic functional construct that underlies motivational impairments in a wide array of mental disorders. These findings provide empirical support to previous frameworks based on narrative reviews (e.g., Knutson & Heinz, 2015; Le Heron, et al., 2019) and go beyond previous case-control meta-analyses focusing on lower-level dimensions of psychopathology (e.g., Keren, et al., 2018; Radua, et al., 2015; W. N. Zhang, et al., 2013).

At the anticipation stage, our findings revealed that both reward anticipation and loss anticipation consistently involve the VS, AI, and SMA in both healthy and clinical/at-risk conditions. These findings echo recent meta-analyses on healthy samples (e.g., Dugre, et al., 2018; Gu, et al., 2019; Oldham, et al., 2018; Wilson, et al., 2018) and extend previous observations to the clinical/at-risk conditions. It is thus likely that the VS-related network is implicated in signaling salience of an upcoming event rather than encoding expected positive incentive value (Oldham, et al., 2018). This conjecture is supported by the evidence showing that the level of VS activation is increased in proportion to the degree of stimulus saliency regardless of valence (Seymour, Daw, Dayan, Singer, & Dolan, 2007; Zink, Pagnoni, Chappelow, Martin-Skurski, & Berns, 2006; Zink, Pagnoni, Martin-Skurski, Chappelow, & Berns, 2004; Zink, Pagnoni, Martin, Dhamala, & Berns, 2003). Considering the key role of the VS in motivational salience, it is convincible that there are similar VS dysfunctions between reward anticipation and loss anticipation, although previous studies have mainly emphasized the role of VS disruptions in reward processing deficits (e.g., Radua, et al., 2015; B. Zhang, et al., 2016).

Indeed, the current study provided the first meta-analytic evidence showing that there is a common blunted VS activity in response to anticipation of both reward and loss across multiple neuropsychiatric conditions (e.g., schizophrenia, major depressive disorder, and substance use disorders). Aberrant VS activation in both reward and loss anticipation indicates a valence-independent alteration in neural systems involved in approach and avoidance (see also Leknes & Tracey, 2008; Spielberg, et al., 2012). In line with the current findings, recent brain imaging studies employing a dimensional approach have demonstrated attenuated VS responses to reward across a wide range of clinical diagnoses (Arrondo, et al., 2015; Hagele, et al., 2015; A. Li, et al., 2020; Satterthwaite, et al., 2015). Moreover, VS activation scales with anhedonia scores or overall depression severity across clinical diagnostic categories (e.g., Arrondo, et al., 2015; Corral-Frias, et al., 2015; Hagele, et al., 2015; Keren, et al., 2018; Satterthwaite, et al., 2015) and predicts individual differences in approach motivation in general populations (Hahn, et al., 2009; Hahn, et al., 2011). Together, the common VS hypoactivity to reward/loss anticipation might be a brain phenotype underlying the pathophysiology of motivational deficits (e.g., anhedonia and apathy) spanning categories of mental disorders. The impairments in salience processing could help explain motivation-related symptoms associated with not only rewarding but also aversive signaling (Howes & Nour, 2016; Serranova, et al., 2011). The shared alterations of motivation-related brain systems might be attributed to common genetic or environmental risk factors for motivational symptomatology in neuropsychiatric conditions (Buckholtz & Marois, 2012; Corral-Frias, et al., 2015).

We next demonstrated that the VS, which exhibited transdiagnostic hypoactivation in response to reward and loss anticipation, served as one of the key nodes in a distributed brain network encompassing multiple lesion locations causing motivational impairments. Noteworthy, the lesion network mapping establishes the causal relationship between brain and behavior from the perspective of large-scale brain networks rather than isolated brain regions (Fox, 2018). Therefore, the identified network overlap in the VS does not indicate that this region alone plays a casual role in determining motivational impairments. Instead, the results demonstrate that the VS represents a key node in a large-scale network in which multiple brain regions work together to support motivational functioning. The lesion network mapping findings thus complement our meta-analytic results in several essential aspects. First, these findings establish a causal relationship between the VS showing common hypoactivity to reward/loss anticipation and motivation-related symptoms, providing empirical support to previous frameworks (e.g., Husain & Roiser, 2018; Le Heron, et al., 2019). Second, our findings are the first to demonstrate that despite being heterogeneous in their anatomical localizations, lesions causing motivational deficits are located within a distributed network with shared functional connectivity to the VS (Groenewegen & Trimble, 2007; Park, et al., 2019). These results suggest that the VS is a central hub within the human motivation system. In line with the idea, the VS engages rich structural and functional connectivity with multiple subcortical and cortical brain regions and functions as the crossroad between limbic, cognitive, and motor systems (Groenewegen & Trimble, 2007; Groenewegen, Wright, Beijer, & Voorn, 1999; Park, et al., 2019). Together, our lesion network mapping findings not only provide converging evidence on the key role of VS in motivational deficits, but also highlight the importance of large-scale brain networks in the pathophysiology of disorder-spanning motivational dysfunction. This is in line with a recent connectome-wide association study showing that dimensional reward deficits across mental disorders are characterized by dysconnectivity of the VS with large-scale functional networks (Sharma, et al., 2017).

Regarding the consumption stage, our findings revealed consistent involvement of the VS and vmPFC for both healthy controls and clinical/at-risk conditions, in line with previous evidence showing that these regions are important for reward consumption (Diekhof, et al., 2012; Oldham, et al., 2018). However, it should be noted that much fewer studies have reported the results of the loss consumption, which impedes the investigation of the roles of these regions in processing loss outcomes. Moreover, our results did not reveal consistent differences in the engagement of these regions between groups, suggesting that the consumption phase might be less susceptible to various neuropsychiatric conditions. Indeed, it has been proposed that motivation-related symptoms might be mainly driven by anticipatory deficits rather than by hedonic deficits (Nusslock & Alloy, 2017; Treadway, 2016; Treadway & Zald, 2011). Nevertheless, we identified consistent IPL hyperactivation in MID reward consumption phase across neuropsychiatric conditions. Although the IPL is not commonly recognized as a typical node within the human motivation system, this region has been implicated in integrating reward and other factors into a unified value representation (MacKay, Blum, & Mendonca, 1992; Parr, Coe, Munoz, & Dorris, 2019; Stanford, et al., 2013). In accordance, striatal functional connectivity with the IPL is altered across multiple mental disorders (Marchand, et al., 2011; J. T. Zhang, et al., 2018). Therefore, future studies are needed to examine psychological functions and clinical significance associated with the IPL hyperactivation during the consumption phase. That being said, it should be noted that the current findings on the IPL hyperactivation should be interpreted with caution due to the reason that the results were not validated by the LOEO analysis and modulated by demographic variables.

Several limitations relevant to the current study should be acknowledged. First, the limited number of experiments for each neuropsychiatric condition precluded the possibility to examine diagnosis-specific alterations in the brain (Barch, 2020; Fusar-Poli, 2019), but statistical power for investigation of both common and distinct abnormalities will increase for future meta-analyses owing to a rapidly growing literature on dimensional psychiatry. Both specific and nonspecific neural correlates are important to a more comprehensively understanding of the hierarchical psychopathology structure, which could help to explain both comorbidity and heterogeneity across mental disorders (Zald & Lahey, 2017). Second, although the MID task has been extensively deployed in the literature, the task cannot achieve the full picture of motivational processes; for instance, this task did not allow for capturing reward prediction error signals (Oldham, et al., 2018; Wilson, et al., 2018). Third, the numbers of included experiments for different neuropsychiatric conditions and experimental contrasts are not well balanced, but modulation analyses demonstrated that our main findings were not modulated by diagnoses. Finally, modulating effects of potentially influential factors such as illness duration could not be assessed comprehensively as this information was not consistently included across primary studies.

To sum up, the current study examined functional disruptions in neural circuitry underlying motivational processing across multiple diagnoses, combining a meta-analysis on brain imaging studies of MID and a lesion network mapping approach. Our findings implicate a common VS-based network of motivation-related deficits in multiple neuropsychiatric conditions. These findings suggest that the encoding of motivational salience in the VS during reward/loss anticipation represents a key functional construct of mental health, the dysfunction of which is a cross-diagnostic domain giving rise to disorder-spanning motivation-related symptoms. Our findings complement recent evidence showing transdiagnostic overlap at multiple units of measurement, ranging from symptoms (Caspi, et al., 2014; Lahey, et al., 2012) and psychological functions (McTeague, Goodkind, & Etkin, 2016) to brain morphology (Goodkind, et al., 2015; Rashid & Calhoun, 2020; Sha, Wager, Mechelli, & He, 2018), brain functions (Feng, et al., 2018; Hamilton, Chen, Waugh, Joormann, & Gotlib, 2015; McTeague, et al., 2017; McTeague, et al., 2020), and genetic factors (Consortium, 2018). Finally, our findings provide possible candidate brain phenotypes (i.e., the VS and its associated network) for future work on neuromodulatory, pharmacological, and clinical interventions across types of psychopathology.

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**Figure 1. Significant clusters from the main meta-analysis of reward anticipation in (A) healthy controls, (B) clinical/at-risk** **conditions and (C) hypoactivation of clinical/at-risk** **conditions relative to healthy controls (cluster-level family-wise error correction, *P* < 0.05, with a cluster-forming threshold of *P* < 0.001 using 10,000 permutations).** **(A).** Consistent maxima in the bilateral VS (extending to the amygdala, thalamus, and AI), SMA, precentral gyrus, middle occipital gyrus, and right calcarine were identified for healthy controls. **(B).** Consistent maxima in the bilateral VS and AI were identified for clinical/at-risk conditions. **(C).** Consistent maxima in the bilateral VS were found for hypoactivation of clinical/at-risk conditions relative to healthy controls.



**Figure 2. Significant clusters from the main meta-analysis of loss anticipation in (A) healthy controls, (B) clinical/at-risk** **conditions, and (C) hypoactivation of clinical/at-risk** **conditions relative to healthy controls (cluster-level family-wise error correction, *P* < 0.05, with a cluster-forming threshold of *P* < 0.001 using 10,000 permutations).** **(A).** Consistent maxima in the bilateral VS (extending to the amygdala, thalamus, and AI) and SMA were identified for healthy controls. **(B).** Consistent maxima in the bilateral VS, AI, SMA, thalamus, and precentral gyrus were identified for clinical/at-risk conditions. **(C).** Consistent maxima in the left VS, middle occipital gyrus, and cuneus were found for hypoactivation of clinical/at-risk conditions relative to healthy controls during loss anticipation.



**Figure 3. Significant clusters from the main meta-analysis of reward consumption in (A) healthy controls, (B) clinical/at-risk conditions, and (C) hyperactivation of clinical/at-risk conditions relative to healthy controls (cluster-level family-wise error correction, *P* < 0.05, with a cluster-forming threshold of *P* < 0.001 using 10,000 permutations).** **(A).** Consistent maxima in the bilateral VS, vmPFC, and PCC were identified for healthy controls. **(B).** Consistent maxima in the vmPFC and right VS were identified for clinical/at-risk conditions. **(C).** Consistent maxima in the left IPL were found for hyperactivation of clinical/at-risk conditions relative to healthy controls during reward consumption.



**Figure 4. The conjunction analyses for common regions for clinical/at-risk conditions and healthy controls. (A).** Consistent maxima in the bilateral VS, vmPFC, and PCC were identified for overlap of activation between clinical/at-risk conditions and healthy controls during reward anticipation. **(B).** Consistent maxima in the bilateral VS and vmPFC were identified for overlap of activation between clinical/at-risk conditions and healthy controls during loss anticipation. **(C).** Consistent maxima in the bilateral VS and vmPFC (yellow) were identified for overlap of conjunction results from **A** (red) and **B** (green). **(D).** Consistent maxima in the bilateral VS and vmPFC were identified for overlap of activation between clinical/at-risk conditions and healthy controls during reward consumption.



**Figure 5. The conjunction analyses for common regions for clinical/at-risk conditions vs. healthy controls as well as lesion network results. (A).** Consistent maxima in the left VS were identified in the hypoactivation in clinical/at-risk conditions relative to controls during reward and loss anticipation conjunction analysis. **(B).** Bilateral VS and ACC were identified for theoverlap of lesion-derived networks (75%). **(C).** The conjuction (yellow) between results from **A** (red) and **B** (green).

**Table 1. A summary of clinical/at-risk conditions included in meta-analyses**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Clinical/at-risk conditions** | | **Reward Anticipation** |  | **Reward Anticipation** |  | **Reward Anticipation** |  | **Reward Consumption** |  | **Reward Consumption** |  | **Reward Consumption** |  | **Loss Anticipation** |  | **Loss Anticipation** |  |
| **NC** |  | **HC vs NC** |  | **NC vs HC** |  | **NC** |  | **HC vs NC** |  | **NC vs HC** |  | **NC** |  | **HC vs NC** |  |
| **Addicction-related** | alcohol-dependence | 8 |  | 3 |  | 2 |  | 4 |  | 1 |  | 1 |  | 6 |  | 2 |  |
| cannabis users | 1 |  | 2 |  | 3 |  | 1 |  | 1 |  | 1 |  | 1 |  | 0 |  |
| cocaine-dependence | 1 |  | 2 |  | 1 |  | 2 |  | 0 |  | 1 |  | 1 |  | 2 |  |
| nicotine smokers | 1 |  | 0 |  | 0 |  | 0 |  | 0 |  | 0 |  | 1 |  | 0 |  |
| pathological gambling | 2 |  | 3 |  | 3 |  | 3 |  | 2 |  | 2 |  | 1 |  | 3 |  |
|  | anxiety disorders | 0 |  | 1 |  | 2 |  | 0 |  | 0 |  | 1 |  | 0 |  | 0 |  |
| **Mood/Anxiety-related** | bipolar disorder | 2 |  | 3 |  | 0 |  | 1 |  | 1 |  | 0 |  | 2 |  | 0 |  |
| early life stress | 0 |  | 1 |  | 0 |  | 0 |  | 0 |  | 0 |  | 0 |  | 0 |  |
| major depressive disorder | 4 |  | 3 |  | 4 |  | 4 |  | 5 |  | 1 |  | 4 |  | 2 |  |
| obsessive-compulsive disorder | 2 |  | 1 |  | 0 |  | 1 |  | 1 |  | 1 |  | 1 |  | 1 |  |
| rumination symptoms | 0 |  | 0 |  | 1 |  | 0 |  | 0 |  | 0 |  | 0 |  | 0 |  |
| **Neurodevelopmental disorders** | attention deficit hyperactivity disorder | 5 |  | 8 |  | 2 |  | 1 |  | 1 |  | 4 |  | 1 |  | 5 |  |
| autism spectrum disorder | 0 |  | 3 |  | 2 |  | 0 |  | 2 |  | 3 |  | 0 |  | 0 |  |
| **Psychosis** | high risk for psychosis | 1 |  | 1 |  | 2 |  | 0 |  | 0 |  | 0 |  | 1 |  | 1 |  |
| schizophrenia | 4 |  | 5 |  | 0 |  | 2 |  | 1 |  | 1 |  | 3 |  | 1 |  |
| subclinical psychotic experiences | 1 |  | 1 |  | 0 |  | 0 |  | 0 |  | 0 |  | 0 |  | 0 |  |
| **Personality-related** | borderline personality disorder | 1 |  | 0 |  | 0 |  | 0 |  | 0 |  | 0 |  | 1 |  | 0 |  |
| external disorder (mainly oppositional defiant disorder) | 1 |  | 0 |  | 0 |  | 1 |  | 0 |  | 0 |  | 0 |  | 0 |  |
| high sociodemographic risk for antisocial behaviors | 1 |  | 1 |  | 0 |  | 1 |  | 0 |  | 0 |  | 1 |  | 1 |  |
| **Eating disorders** | binge eating disorder | 0 |  | 0 |  | 1 |  | 0 |  | 0 |  | 1 |  | 0 |  | 0 |  |
| obesity | 0 |  | 1 |  | 1 |  | 0 |  | 0 |  | 0 |  | 0 |  | 0 |  |
| **Others** | body focused repetitive behaviors | 0 |  | 0 |  | 1 |  | 0 |  | 0 |  | 0 |  | 0 |  | 0 |  |
| Huntington's disease | 2 |  | 0 |  | 0 |  | 0 |  | 0 |  | 0 |  | 2 |  | 0 |  |
| impulsivity traits | 0 |  | 1 |  | 0 |  | 0 |  | 0 |  | 0 |  | 0 |  | 0 |  |

**HC – healthy controls, NC - Neuropsychiatric conditions**