Trans-Diagnostic Structural Imaging in Psychosis: A Comparison Across Schizophrenia, Frontotemportal Dementia, and Alzheimer's Dementia

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ABSTRACT

Psychotic symptoms, a key feature of Schizophrenia, can have a significant impact on safety and quality of life for patients. Despite years of research, the pathophysiology of psychotic symptoms has not been fully elucidated, and this has frustrated efforts to improve their treatment. In this project we took advantage of the fact that psychotic phenomena are present in a number of disorders, with the aim of determining which brain regions remain associated with psychotic phenomena across disorders. These regions could then be thought of as constituting a 'core' part of the network underlying psychosis and might serve as more targeted loci for future pathophysiological and therapeutic research. We examined the structural MRI data for 322 subjects (including patients with psychosis, disease controls, and healthy controls) pooled from three databases: Schizconnect (schizophrenia); GENFI (Fronto-temporal dementia) and ADNI (Alzheimer's Dementia and Mild Cognitive Impairment). Images were preprocessed using BPIPE and then processed using CIVET to produce cortical thicknesses and MAGeTbrain to produce subcortical volumes. For statistical analysis, GLM was used and covariates chosen were age, sex, diagnosis, and site. The Surfstat analytics package was used to examine cortical thickness; no regions were found to be significantly different between psychotic and non-psychotic subjects using standard corrections for repeated measures, but in exploratory analysis the anterior cingulate cortex was found to be significant using $p = 0.005$ uncorrected. In subcortical regions, reduced bilateral thalamus and striatum volume, but not globus pallidus, or hippocampus and its subfields, were found to be predicted by the presence of psychosis. This suggests that these subcortical structures, both long associated with psychosis, may be a common 'point of failure' leading to the onset of psychosis. Methodological limitations, such as poor scan quality and the challenges of combining data from disparate databases, are also discussed. In

summary, there do seem to be primarily subcortical brain regions which underlie psychotic symptoms across disorders, but further research with datasets aimed at completing this picture is required.

Les symptômes psychotiques, une caractéristique clé de la schizophrénie, peuvent avoir un impact significatif sur la sécurité et la qualité de vie des patients. Malgré des années de recherche, la physiopathologie des symptômes psychotiques n'a pas été entièrement élucidée, ce qui a entravé les efforts visant à améliorer leur traitement. Dans ce projet, nous avons profité du fait que les phénomènes psychotiques sont présents dans un certain nombre de troubles, dans le but de déterminer quelles régions du cerveau restent associées aux phénomènes psychotiques à travers les troubles. Ces régions pourraient alors être considérées comme constituant une partie « noyau » du réseau sous-jacent à la psychose et pourraient servir de loci plus ciblés pour de futures recherches physiopathologiques et thérapeutiques. Nous avons examiné les données d'IRM structurelles de 322 sujets (y compris des patients atteints de psychose, des témoins de la maladie et des témoins sains) regroupées à partir de trois bases de données : Schizconnect (schizophrénie) ; GENFI (démence fronto-temporale) et ADNI (démence Alzheimer et déficience cognitive légère). Les images ont été prétraitées à l'aide de BPIPE puis traitées à l'aide de CIVET pour produire des épaisseurs corticales et MAGeTbrain pour produire des volumes sous-corticaux. Pour l’analyse, le GLM a etait utilisé, est les covariables choisies étaient l'âge, le sexe, le diagnostic et le site. Le logiciel d'analyse Surfstat a été utilisé pour examiner l'épaisseur corticale ; aucune région ne s'est avérée significativement différente entre les sujets psychotiques et non psychotiques en utilisant des corrections standard pour les mesures répétées, mais dans l'analyse exploratoire, le cortex cingulaire antérieur s'est avéré significatif en utilisant $p = 0,005$,

non corrigé. Dans les régions sous-corticales, une réduction du volume bilatéral du thalamus et du striatum, mais pas du globus pallidus, ou de l'hippocampe et ses divisions, était prédite par la présence d'une psychose. Cela suggère que ces structures sous-corticales, toutes deux associées depuis longtemps à la psychose, peuvent être un « point d'échec » commun menant à l'apparition de la psychose. Les limitations méthodologiques, telles qu'une mauvaise qualité d'analyse et les défis de combiner des données provenant de bases de données disparates, sont également discutées. En résumé, il semble y avoir des régions cérébrales surtout sous-corticale qui sous-tendent les symptômes psychotiques à travers les troubles, mais des recherches supplémentaires avec des ensembles de données visant à compléter ce tableau sont nécessaires.

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CONTRIBUTION TO ORIGINAL KNOWLEDGE

This thesis is one of only a few scholarly works that directly compare schizophrenia to other conditions in which psychosis is present, and the only one, to our knowledge, that directly compares it to two other conditions- Alzheimer's Dementia and Fronto-Temporal Dementia. These conditions are characterized by more advanced neurological degeneration in regions in many cases similar to those found to have less extreme deficits in schizophrenia. While psychosis has different phenomenology in each of these disorders there can be overlap, and the core symptom of disconnection of percepts or beliefs from reality does occur in each disorder when psychotic symptoms are present. As such, the finding that the striatum and thalamus- regions long associated with symptoms in schizophrenia- seem to be two of the few regions with decreased volume or thickness across all three of these disorders speaks to a special role for them in terms of the altered information processing which subtends psychotic phenomena. In addition, the methodological challenges faced while conducting this analysis lead to insights about how future studies aimed at trans-diagnostic imaging analysis may be conducted in order to improve the quality of research.

CONTRIBUTION OF AUTHORS

I, David Benrimoh, am the sole author of this thesis. The contributions of the many people who supported this work are listed in the acknowledgments. I would, however, like to recognize my supervisors Dr. Ducharme and Dr. Misic for their comments on this thesis.

1. INTRODUCTION

1.1 Psychosis

Psychosis is defined as a loss of contact with reality (NIMH, 2021). It can take many forms, including auditory hallucinations and/or visual hallucinations, delusions, or disorganized thought, and is a key part of the diagnosis of Schizophrenia (APA, 2013). While psychosis may not be the most important predictor of functional outcome in Schizophrenia (Bowie and Harvery, 2006), its treatment is critical for ensuring safety, quality of life, and in supporting vocational function (Wiersma et al., 2004; Shawyer et al., 2003; Mucci et al., 2021). Psychotic symptoms can cause patients and family members significant distress and can negatively impact attempts to provide mental healthcare (Shawyer et al., 2003; Wittorf et al., 2009).

Thankfully, pharmacological treatments exist which help reduce psychotic symptoms, generally via the blockade of dopamine in the mesolimbic pathway (though this picture is more complicated in the case of the atypical antipsychotics, which have effects on multiple neurotransmitters) (Brisch et al., 2014). Unfortunately, antipsychotic treatment is not effective for all patients (Potkin et al., 2020). This has spurred research into the pathophysiology of psychotic syndromes, with the hope that better mechanistic understanding will improve our ability to design new treatments (Stepnicki et al., 2018).

Many approaches can be taken with this objective in mind. Significant focus has been placed on using neuroimaging to identify brain regions involved in psychosis, and on using functional neuroimaging techniques and tracer studies to better understand differences in the structure and function of the brain in patients with schizophrenia compared with healthy controls,

or in patients at early and later stages of schizophrenia. The findings from these studies will be discussed below in the literature review section. A limitation of these studies, however, is the fact that schizophrenia includes many more symptoms than just psychosis, and it is very likely that these other symptoms are caused by brain changes which, while they may be related to psychosis, are not themselves causes of psychosis, given that symptoms such as negative and cognitive symptoms can persist even after the resolution of a psychotic episode and remain a source of disability (Buchanan, 2007).

1.2 Psychosis across disorders

Psychosis is not itself limited to Schizophrenia- rather, it is a syndrome which can be found in a number of other conditions, both within the psychiatric disorders (i.e. bipolar disorder (APA, 2013); borderline personality disorder (Paris, 2007)) and in other conditions, such as dementia (Marcinkowska et al., 2020), Parkinson's disease (Thanvi et al., 2005) and as a result of various substances (Wilson et al., 2018).

The fact that psychotic symptoms are present in a number of disorders presents an intriguing possibility: while *within* disorder it may be a challenge to abstract out brain regions related specifically to psychosis, looking *between* disorders may help identify which brain regions are specific to psychosis. The hypothesis then is that there are certain brain regions which *must* have structural or functional abnormalities in order for the psychotic state to obtain; the research question then becomes to determine if such regions can be identified when engaging in a transdiagnostic analysis. Should such regions be found, then the hypothesis would be supported and a common set of regions involved specifically in the generation of the psychotic

state would become grounds for potentially useful future research; should such regions not be found, given an adequate dataset and appropriate methods, then the hypothesis could be rejected and the conclusion arrived at that psychosis, while similar from a behavioral standpoint, is neurobiologically distinct in different conditions.

This was the rationale for and objective of my master's project: to determine if there exists a common set of regions subtending psychosis across diagnoses. While the hypothesis provided above appears simple, in practice there are a number of caveats and assumptions that must be addressed before proceeding further. First, we must justify why it is reasonable to hypothesize that the psychotic symptoms in different disorders may have common underlying neurobiological causes. The second question to consider is which imaging modality is to be used. The third question to address is *which* conditions one should choose to study trans-diagnostically. This leads to the fourth consideration, which is a discussion of the phenomenology of psychotic symptoms which are found in each of the chosen disorders, and how differences between these might inform the analysis, expected results, and their interpretation.

Psychosis is a syndrome- a state defined by a collection of related symptoms, rather than a singular clinical entity. As noted above, one might argue that the key underlying 'essence' of psychosis is the disconnection between percepts and beliefs and external reality. It is only by taking this view that it becomes possible to consider the disparate possible psychotic symptoms as being part of one cohesive syndrome with potentially common elements of underlying neurobiology. This is important because while visual and auditory hallucinations and delusions

have some similar findings in the literature, they have also been shown to have unique findings (see literature review section) and to occur at different frequencies- and with varying phenomenology- in different disorders, as will be discussed in section 1.5. As such, without this organizing principle of disconnection of percepts and beliefs from reality, it may seem tenuous to try and determine which neurobiological alterations are specific to the psychotic syndrome. Thankfully, we do not need to rely only on this logic, as there is another piece of evidence that links together psychotic symptoms across disorders: treatment. While not every patient will benefit and while care must be taken to avoid side effects, the symptomatic treatment for psychosis regardless of underlying diagnosis, is often achieved with antipsychotics (Brodaty et al., 2003; AFTD, 2021; Klein et al., 2003; Patel et al., 2014). Even within disorders, such as in schizophrenia, antipsychotic treatments generally improve hallucinations as well as delusions (Chokhawala et al., 2020). As such, it seems reasonable to make the assumption that the psychotic syndrome can be investigated as an entity, while at the same time keeping in mind the caveat that there are likely mechanisms related to the modality of the psychotic symptom which are unique to that symptom (e.g. Frith, 2005) and that as such any mechanistic explanation focusing on the psychotic syndrome or phenotype is necessarily a limited one.

1.3 Imaging Modality

We next come to the question of imaging modality. As is discussed below, important findings have been described for psychosis in most imaging modalities, including structural and functional magnetic resonance imaging (sMRI and fMRI, respectively); positron emission tomography (PET); and diffusion tensor imaging (DTI). Ideally, we would perform a study that correlates findings across imaging modalities (e.g. Lerman-Sinkoff et al., 2019). This is

important, as in many cases one modality can compensate for the weaknesses of another modality- such as using the superior temporal resolution of electroencephalography (EEG) to supplement the poor temporal but relatively better spatial resolution of fMRI (Mulert, 2013); in addition, findings not present in one modality may be apparent in another modality- for example, if altered functioning is not apparent as a structural change in sMRI, it may still be appreciable on fMRI. However, here pragmatism must also play a role as not all datasets have access to multiple imaging modalities, and often imaging modalities which go beyond structural imaging may employ task designs that differ enough between studies to limit the ability to compare them (though this challenge may be mitigated when using resting state imaging protocols). As such for this study, which as I discuss is the first of its kind to compare schizophrenia to two neurodegenerative diseases, I chose to focus on structural imaging, i.e. sMRI. One key benefit of sMRI is that while grey matter reductions are present in schizophrenia (see section 1.4) they are often not of the same severity as those seen in neurodegenerative conditions where similar regions are affected. As such, careful choice of the comparator conditions could allow for conditions with more 'exaggerated' versions of the deficits seen in schizophrenia to be compared to it in order to determine which of the more subtle deficits in schizophrenia are most likely to be related to psychosis.

1.4 Comparator Diseases

This brings us to the choice of comparator diseases. For this study, I chose fronto-temporal dementia (FTD), Alzheimer's dementia (AD), and Parkinson's disease (PD), in addition to schizophrenia (Scz). FTD is characterized by a fronto-temporal pattern of degeneration, with involvement of other regions, such as the striatum, in some patients (Mann et al., 1993); AD by

early deterioration of the medial temporal lobe including the hippocampus, in many cases followed by deterioration of other cortical areas, such as prefrontal cortex (Serrano-Pozo et al., 2011); and Parkinson's by degeneration of the basal ganglia (Dickson, 2018). These patterns are interesting because, as will be discussed below, both frontal and temporal changes as well as dysregulation in the striatum can be found in schizophrenia. The potential presence of psychosis in all four of these conditions point to a potential common failure state which, though beginning from different areas of degeneration, leads to the same (or at least similar) experienced symptoms. As such, comparing them may improve our chances of finding the 'core' set of structural changes subtending psychosis. However, before we can decide to compare these four disorders, it is worth spending some time on a discussion of the phenomenology and patterns of psychotic symptoms in each.

Of note, due to poor scan quality and a resulting insufficient number of scans of psychotic patients, we were required to remove PD from the analysis. This will be discussed in the methods and results sections. However, for completeness we will also review psychotic symptomatology in PD. I also note that, for the purposes of this discussion, we will omit disorganized thought and behavior; though this is classified as a positive symptom (APA, 2013), it can occur independently of hallucinations and delusions, and disorganized behavior can occur for a number of nonpsychotic reasons in the disorders being considered (e.g. Müller-Spahn, 2003), limiting its feasibility as a symptom of interest in the context of a trans-diagnostic approach. As such, the discussion of psychosis here and in the rest of the thesis will focus on the most common clearly psychotic symptoms across the four disorders: auditory and visual hallucinations and delusions. In addition, I will discuss the common phenomenology of the

symptoms themselves and not of their onset, as a very rich literature exists on the topic of onset phenomenology, particularly in early or prodromal schizophrenia (see Larson et al., 2010 and Thompson et al., 2018 for a review), and this is out of the scope of this thesis.

1.5 Psychosis Phenomenology Across Comparators

As a better understanding of schizophrenia treatment motivated this work, we will begin with a description of psychosis in schizophrenia. The most common single-sensory-modality hallucinatory symptom in schizophrenia is auditory hallucinations, often auditory verbal hallucinations (i.e. the hallucinations of voices speaking), with 60-80% (Waters et al., 2014) of patients experiencing these; despite this, multimodal hallucinations, most often combining visual and auditory hallucinations, are very common. Indeed, some accounts demonstrate that multimodal hallucinations are more common than unimodal hallucinations, with up to 53% experiencing multimodal hallucinations, with the most common being some combination of auditory and visual hallucinations; however, only roughly 5% experienced solely visual hallucinations (Lim et al., 2016). Some phenomenology of auditory hallucinations, such as hearing multiple voices referring to or commenting on a patient in the third person, hearing one's thoughts being spoken aloud, or having a running commentary of the patient's actions, are considered to be 'classical' symptoms and are referred to as Schneiderian First Rank Symptoms; while these seem to be specific to schizophrenia, they do not occur reliably in all patients with schizophrenia and relying on them can result in low sensitivity when diagnosing the disorder according to a Cochrane systematic review (Soares-Weiser et al., 2015). A potentially more reliable feature of verbal hallucinations in schizophrenia is their negative, critical or abusive character, with the majority of patients experiencing these at least part of the time (Nayani &

David, 1996), and with the negative content of hallucinations being linked to distress (Larøi et al., 2019). Roughly three quarters of patients with schizophrenia will experience delusions, and for more than 50% of patients these will be chronic in nature (Harrow & Jobe, 2010), and most commonly these delusions have persecutory themes (though a variety of delusions, including negative or extremely positive beliefs about the self can also be seen) (see Bentall et al., 2001, for a review). Much has been written about the potential causal mechanisms for delusions and hallucinations, (Bentall et al., 2001; Benrimoh et al., 2018); this is too extensive to review here, but relevant literature will be referenced during the discussion of the results. In summary, a simplified conceptualization of psychotic symptoms in schizophrenia, for the purposes of the comparison in this thesis, is the following: patients with schizophrenia commonly experience negatively valenced or persecutory auditory hallucinations and delusions, and a majority of them will at some point also experience multimodal hallucinations with auditory-visual hallucinations being common.

In Parkinson's disease, roughly one third of patients will experience some psychotic symptom (Thanvi et al., 2005). While psychotic symptoms may in some patients likely be related to antiparkinsonian medications (Thanvi et al., 2005), these are not the sole causes- indeed, hallucinations in PD were recognized as clinically important in this disease prior to the advent of L-dopa treatment (Thanvi et al., 2005) and patients with hallucinations did not differ in terms of antiparkinsonian drug burden from those without hallucinations in an interesting study employing a Cox proportional hazards model (Merims et al., 2004); while this does not rule out the causal effect of drugs, it does suggest that drugs likely must interact with other factors in order to precipitate hallucinations (Thanvi et al., 2005). Other risk factors, such as older age,

longer disease length, depression, and disordered sleep have been associated with psychosis in PD (Thanvi et al., 2005). Thanvi et al., 2005, describe the hallucinations in PD as being mostly visual, usually consisting of animals, people or objects; they are generally non-threatening at the start, and insight is often preserved. However as the disease progresses insight can be lost and this can lead to distress or dangerous behavior. The visual hallucinations occur more frequently when lighting conditions are poor (indicating the importance of a reduction in sensory fidelity which will be discussed below). Auditory hallucinations can occur but are rare, and seem to occur when the disease is more severe (Thanvi et al., 2005). Delusions are most often paranoid in nature- a review of 184 case reports of PD delusions demonstrated that paranoid delusions occurred 82.6% of the time; themes included persecution and delusional jealousy (Warren et al., 2018). Classical misidentification syndromes, such as Fregoli and Capgras, were less common at 11.4% (Warren et al., 2018). In summary, PD psychosis is characterized by initially non-threatening but often eventually distressing or behavior altering visual hallucinations as well as paranoid delusions and infrequent auditory hallucinations.

Moving to frontotemporal dementia, there seems to be less of a clear characterization of common psychotic phenomenology, likely because this phenomenology differs based on the genetic FTD subgroup. Shinagawa et al., 2014, reviewed the literature and estimated a roughly 10% prevalence of psychotic symptoms, but noted that this may be enriched in patients with the C9ORF72 and GRN mutations. In a case series of 7 psychotic patients with the C9ORF72 mutation and one untested but affected sibling, Kertesz et al., 2013 found a mix of symptoms: visual hallucinations (often of people, with whom the patients conversed); as in PD these seemed to be more prevalent in the dark or in low light; in two cases auditory hallucinations, which

consisted of conversations had with visual hallucinations; and paranoid delusions. It should be noted that 3 of their 8 cases had previous psychiatric history, including psychosis, which makes it a challenge to definitively attribute the symptoms to FTD. They also noted paranoid delusions in five non-carriers of the C9ORF72 gene with themes of theft and concerns that spouses had been unfaithful. Somatic delusions are also common in FTD (Ducharme et al., 2017). As such, FTD seems to be able to produce visual and auditory hallucination, as well as paranoid delusions. Indeed, another review of cases noted that FTD can present as schizophrenia-like psychosis when the disease onsets at an early age (Velakoulis et al., 2018).

Finally, in Alzheimer's disease, delusions and hallucinations are frequent- occurring in roughly 50% of patients, occurring more frequently as the disease progresses (Murray et al., 2014). As in PD, visual hallucinations are the most common sensory modality in AD psychosis (Murray et al., 2014), though auditory hallucinations do occur. As in PD and as we see in the case series in FTD, visual hallucinations in AD have been shown to be related to reduced quality of visual information- indeed, they have been directly correlated with abnormalities in the visual system (Holroyd & Sheldon-Keller, 1995). Delusions include paranoid or persecutory beliefs, or beliefs that a spouse is being unfaithful or that theft is occurring; misidentification delusions, such as a patient starting to believe that they are not in their home, also occur (Jeste & Finkel, 2000; Murray et al., 2014; Thanvi et al., 2005). Delusions however are usually not about complex plots or bizarre ideas (i.e. that aliens are somehow involved in the patient's life); this distinguishes the psychosis in AD from schizophrenia somewhat (Jeste & Finkel, 2000) (though we note that psychosis in schizophrenia is not necessarily bizarre in content). As such, AD seems to be similar to PD with a preponderance of visual hallucinations, the rare presence of auditory

hallucinations, and delusions of a paranoid and persecutory type (though with content that is often linked more to forgetting (i.e. believing one is being robbed because on has misplaced an item) than to more complex persecutory ideas seen in schizophrenia).

Given these descriptions, we must again ask if it is reasonable to compare these disorders. At first glance, it seems most reasonable to compare FTD and schizophrenia, given their similar symptomatology (though this should be interpreted with caution, given the comparatively small literature on psychosis in FTD and the fact that it remains a more rare occurrence than in the other disorders, potentially due to less involvement of limbic and mesial-temporal structures (Mendez et al., 2008)). In contrast, PD and AD seem more similar, given the preponderance of visual hallucinations; in addition, Jeste & Finkel (2000) argued that due in part to their phenomenological difference with schizophrenia, psychotic symptoms in AD should be considered a separate pathology. However, there are similarities. There is the presence of paranoid delusions in all four disorders, as well as the fact that, while their proportions differ, both auditory and visual hallucinations occur in all four conditions (with multimodal auditory-visual hallucinations actually being very common in schizophrenia). In addition, the specific content of hallucinations and delusions seem to be different between disorders, but this is neither a rule nor does it detract from the fact that negative valence does seem to be predominant. As noted above, antipsychotic medications are a mainstay of treatment in all four conditions. I posit that the precise phenomenology of psychosis in these conditions is different precisely because the disease process leading to psychosis does indeed differ in each condition, meaning that in each disorder different combinations of sensory deficits and maladaptive formation of alterations of prior beliefs obtain; despite these differences, however, each disorder leads to the final step-

the divorcing of percepts and experienced beliefs from observed reality. As I argue and demonstrate via simulation in Benrimoh et al., 2018, this is a fundamental manner in which psychosis can be viewed: as a state where the ability to use sensory information to correct faulty beliefs fails, allowing for maladaptive priors (which may have been shaped or strengthened by the disease process and its negative impact on the ability to process external information) to become dominant and generate hallucinatory percepts (or, by extension, delusional beliefs).

2. LITERATURE REVIEW- COMPARATIVE NEUROIMAGING IN SCHIZOPHRENIA AND OTHER DISORDERS WITH PSYCHOTIC SYMPTOMS

My literature review will consist of two parts. In the first, I will discuss common neuroimaging findings in schizophrenia. This will set the stage for the discussion of results in context of the original disease of interest and is adapted from a review of neurobiology I conducted for Humpston et al., 2019. In the second part, I will discuss the current literature with respect to comparative neuroimaging in examining similarities between schizophrenia and other disorders, as this literature will be most directly relevant to the results and discussion presented here.

2.1 Neuroimaging in Schizophrenia

Structural studies in auditory hallucinations have found reduced grey matter volume in the superior temporal gyrus, which contains Wernicke's area and the primary auditory cortex (Upthegrove et al., 2016; Mørch-Johnsen et al., 2017), and medial and inferior frontal cortex (Upthegrove et al., 2016; Kubera et al., 2014). Alterations in the lateral prefrontal cortical network are present in hallucinating and non-hallucinating patients with schizophrenia, and some

(Kubera et al., 2014) have hypothesized that these alterations interact with those in other frontal, temporal, and insular regions more specific to hallucinations in order to produce the phenomenon; this is thought to occur via alterations in language (temporal, frontal and subcortical), salience (insular) and attention (frontal) networks (Kubera et al., 2014; Palaniyappan et al., 2013; Allen et al., 2012). Reduced gray matter in some of these areas has been directly correlated with symptom severity (Kubera et al., 2014; Allen et al., 2012); structural covariance between frontal, temporal, hippocampal and insular areas have also been correlated with hallucination severity, providing more evidence for a malfunctioning network of language and executive regions responsible for auditory verbal hallucinations (Modinos et al., 2009; Bohlken et al., 2017).

Alterations in white matter tracts have also been demonstrated consistently. In particular, the arcuate fasciculus (AF) has been found to be abnormal in structural (Upthegrove et al., 2016) and diffusion tensor imaging studies (Bohlken et al., 2017; Geoffroy et al., 2014; McCarthy-Jones et. al., 2015; Knöchel et al., 2012; de Weijer et al., 2012). Additionally, amongst the different white matter disturbances present in psychotic patients, AF disturbances seem specific to patients with auditory hallucinations (Gavrilescu et al., 2010), and lower AF integrity is positively correlated with symptom severity (Ćurčić-Blake et al., 2015). Other auditory hallucination-related white matter disturbances have been found in uncinate, thalamic, and corpus callosum tracts (Bohlken et al., 2017).

Dopamine, the target of antipsychotic medication, and key in the functioning of the striatum, has long been associated with hallucinations (Tost et al., 2010; Kapur et al., 2003).

Indeed, schizophrenia patients with delusions have dopamine dysregulation (Howes et al., 2013a and 2013b), though this does not seem to be present in PET studies of healthy voice hearers (Baumeister et al., 2017). Therefore dopamine dysregulation may act as a risk factor for psychotic auditory hallucinations (Tost et al., 2010) but may not always be required for the generation of AVH.

fMRI studies also demonstrate network dysregulation. Studies have shown impaired deactivation of the default mode network during tasks (Upthegrove et al., 2016), and increased connectivity between anterior cingulate and superior temporal cortex during self-generated speech (Mechelli et al., 2007), suggesting a network activated by inappropriate stimuli. The subjective reality of auditory hallucinations was also related to the functional connectivity between auditory cortex, inferior frontal gyrus/Broca's area, the cingulate cortex, the ventral striatum, and other regions, indicating contributions of alterations in motor, sensory, and salience monitoring to the genesis of auditory hallucinations (Raij et al., 2009).

Taken together, these results suggest that auditory hallucination production requires the dysfunction and dysconnection of a distributed network with sensory, motor, attentional/salience, and reality monitoring components. Dysfunction of some brain regions (i.e reduced gray matter) seems to interact with white-matter related dysconnectivity to produce hallucinations, with potentially the mix and identity of the constituent dysfunctional regions having some influence on hallucination content, modality, and form.

We now turn to delusions. In structural imaging, loss of frontal and uncal gray matter integrity has been positively associated with the severity and extent of delusions (Birur et al., 2017). Aberrant subcortical dopamine regulation may be an example of shared pathophysiology between hallucinations and delusions and may underlie cognitive biases similar to both symptoms (Broyd et al., 2017). This theory is supported by the finding of a positive correlation between disruption in prediction-error signals (thought to be encoded by dopamine) and delusional tendencies (Corlett et al., 2007; Murray et al., 2008) and by fMRI studies showing dysfunction of the frontal salience network in schizophrenic patients during reward and learning related tasks (White et al., 2013). There are also consistent reports of decreased hippocampal volume in schizophrenia (though this has not been definitively shown to be specific to delusions) (Birur et al., 2017). Some authors have argued that the high rate of hippocampal atrophy in Alzheimer's dementia patients supports the importance of hippocampal dysfunction in the causation of delusions (Boublay et al., 2016).

fMRI results have supported hyperactivity in a network of cortical midline structures (including medial prefrontal cortex, cingulate cortex, and precuneus) which are positively correlated with delusions of reference; this hyperactivity also separated delusional patients and non-delusional patients and controls (Larivière et al., 2017). In summary, delusions seem to share frontal- and attending salience attribution and executive- dysfunction with auditory hallucinations, while potentially implicating dysfunction of hippocampus- raising the possibility that alterations in memory are important in delusion formation.

Comparatively less information exists about neuroimaging findings for visual hallucinations in schizophrenia (Zmigrod et al., 2016). One fMRI study of patients experiencing a brief psychotic episode (and who therefore who were at risk to but may not have proceeded to develop schizophrenia) demonstrated association of the cuneus, lingual gyrus, and fusiform gyrus with visual hallucinations, and of the anterior insula, occipitotemporal junctions, superior temporal sulcus, and inferior parietal gyrus in the case of audio-visual hallucinations (Jardri et al., 2013). Similar regions, with the notable addition of the hippocampus, were found during fMRI of a single patient with schizophrenia and visual hallucinations (Oertel et al., 2007). What is striking in these findings is the lack of activity in primary visual areas- as opposed to auditory hallucinations which as noted above often seem to associate with auditory cortex- and the potential importance of hippocampal pathology, drawing more parallels with AD, where both visual hallucinations and hippocampal atrophy are common.

2.2 Previous Comparative Neuroimaging Studies

We now move to a discussion of previous work comparing schizophrenia directly to other conditions. Somewhat surprisingly, there seems to be little work in this field when it comes to directly comparing schizophrenia to disorders outside of the primary psychiatric disorders. For example, in the context of visual hallucinations in psychosis, Waters et al., 2014, noted that there remained a lack of clarity in the relationship between visual hallucinations seen in schizophrenia and those seen in neurodegenerative disorders or in eye disease. One study noted that while both patients with schizophrenia and major depression had reductions in hippocampal volume, this reduction was greater in schizophrenia and the difference between the groups became larger with recurrent psychotic illness (Meisenzahl et al., 2010). The largest literature, reviewed by Birur et

al., 2017, is in the comparison between schizophrenia and bipolar affective disorder, likely because these disorders are closely related from a genetic perspective (Craddock & Owen, 2015). Birur et al., 2017, note that grey matter reductions seem to be much less extensive in bipolar disorder than in schizophrenia; hippocampal volume loss occurs in both disorders, but to a lesser extent in bipolar disorder; and a reduction in thalamic volume also appears to be more significant in schizophrenia. They note, however, that often findings in the literature are conflicting. With respect white matter, both disorders seem to have extensive white matter integrity reduction. Finally they note some similarities in terms of alterations in functional networks and some differences, such as lower global connectivity in schizophrenia compared to bipolar disorder. In summary, comparing schizophrenia to other psychiatric disorders does not seem to have clarified our understanding of the neurobiology of psychosis, and there is a dearth of studies comparing schizophrenia to psychosis found in other disorders which may share less of a genetic or developmental overlap with schizophrenia. This in turn supports the rationale of the current work.

In summary, when considering the regions correlated with psychotic symptoms in schizophrenia and also keeping in mind the three disorders to which we will be comparing it, we can hypothesize that certain regions are natural candidates for the hypothesized ‘common pathway’. These include the hippocampus, cingulate cortex, striatum, and various regions of the prefrontal cortex; we will examine if these hypotheses hold true below. In the discussion, we will also examine a computational account of the results, interpreting previous literature on the computational roles of regions found to be common to psychosis across disorders using the

unifying Active Inference framework (Friston et al., 2017). We now turn to a description of study methodology.

3. METHODOLOGY

3.1 Datasets

Four databases were used for the purposes of this project, each corresponding to one of the four conditions being studied. For Schizophrenia, we used the Schizconnect (Wang et al., 2016) database, which is a large online database collecting images from several constituent studies. Given that Schizconnect itself collects images from different studies, it provides a search function to help identify images. We conducted two searches- the first was to identify patients with who has 3T structural MRI imaging, had a strict (DSM-consistent) schizophrenia diagnosis, and who had positive symptom scales available (in order to determine the presence of active or recent auditory and visual hallucinations or delusions); the second was to identify healthy controls with known psychiatric disorder. Patients identified from the search came from two studies. The first was the Centers of Biomedical Research Excellence (COBRE) study, a multi-modal neuroimaging study of 100 patients with Schizophrenia and 100 age-matched controls (Aine et al., 2017). In COBRE, the schizophrenia sample was 81% male and had a mean age of 37.9 (SD = 14) and the healthy control sample was 72% male and had a mean age of 37.5 (SD= 11.8). The second was the Functional Imaging Biomedical Informatics Research Network (FBIRN) study aimed at improving our understanding of the biological basis of clinical symptoms and cognitive dysfunction in Schizophrenia and which recruited 128 patients with Schizophrenia and 128 age- and gender-matched controls (see Potkin & Ford, 2009 for an

introduction and collection of papers). In FBIRN, the schizophrenia sample was 71.9% male, and mean age was 38 (SD = 11.6), and the healthy control sample was 62.5% male with a mean age of 36.2 (SD = 11.9). Both COBRE and FBIRN were multi-site studies. These patients and controls were put into the Scz-Psychosis (Scz-P) and Scz-Healthy Control (Scz-HC) groups, respectively, for our analysis. We did not include a Scz-Disease Control group as we did for the other three disorders. While it is technically possible for a patient to be diagnosed with schizophrenia with only disorganization as positive a symptom (APA, 2013), the high prevalence of hallucinations and delusions make it difficult to expect that one could reliably identify disease controls. In addition, given the poor insight and cognitive symptoms that characterize the disease, recall failure may play a role in any report by a patient that they have never experienced any hallucinations or delusions. Both of these reasons made it challenging to accept that a true disease control group (i.e. patients with a schizophrenia diagnosis but who had not experienced *any* hallucinations or delusions within a year of the scan date) could be reliably identified, and as such we chose to only have a Scz-P and Scz-HC group.

For PD, we used the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data), data for which was collected by a multi-site study aimed at identifying and understanding biomarkers of PD disease progression. This open science database is funded by the Michael J. Fox foundation. It follows a number of cohorts, including patients with *de novo* PD for less than two years and who were not initially on PD medication as well as healthy controls. These two cohorts completed recruitment in 2013 and included 423 patients with PD and 196 controls. After data was downloaded, patients were divided into PD-P, PD-DC, and PD-HC groups.

In AD, we used the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, which has collected data through a number of successive studies (ADNI1, ADNI-GO, and ADNI2). These multi-site studies excluded patients with depression, bipolar disorder, schizophrenia, psychoactive medications which could negatively impair cognition, as well as neurological conditions aside from Alzheimer's dementia (Petersen et al., 2010; nih.gov 2021). These exclusion criteria are important in helping ensure that there are no confounding reasons for psychosis to be present in this dataset. Both studies recruited patients who were cognitively normal, who had mild cognitive impairment (MCI), or who had Alzheimer's dementia. ADNI1 recruited 822 subjects (229 healthy controls, 405 with MCI, and 188 with AD; 58% male, mean age 75); ADNI-GO and ADNI2 added 893 patients, including 184 healthy controls, 564 patients at some stage of MCI, and 145 patients with AD (53% male, mean age 72.5 (SD = 7.2)) (Aisen et al., 2015).

For FTD, we used the Genetic Frontotemporal dementia Initiative (GENFI) database. This study recruits carriers or suspected carriers of FTD-related mutations (MAPT, GRN, or C9orf72); participants in this study could either have symptoms of FTD; be mutation carriers without symptoms; or be non-carriers from affected families (Rohrer et al., 2015). This does mean that some patients in the healthy control group drawn from the GENFI data may have been genetic carriers and at elevated risk of disease; however we decided to include them because they were a minority of the healthy controls in our study (see Table 1) and they were not symptomatic, indicating that key structural changes had likely not yet occurred to the degree required to cause psychosis. Importantly, patients with a psychiatric disease which could

interfere with assessment completion were excluded from GENFI, which helps to limit confounding in this dataset. 317 patients with useable scans were provided from GENFI as part of the data pull provided for this project, of 365 participants (44% male, mean age 50.12, SD = 13.9).

All four databases provided structural MRI images of their participants; most of these images were 3T MRI images, though is some cases (e.g. ADNI; GENFI, see Rohrer et al., 2015) the studies allowed 1.5T scanning when 3T scanning was not available. We were able to restrict the Schizconnect database to return only 3T images as described above.

3.2 Psychosis measures

A key element to consider in preparing this analysis was the definition of psychosis. A number of scales exist for the detection and measurement of psychotic symptoms, and this diversity was reflected in the measures used for each study. ADNI used an expanded version of the neuropsychiatric inventory (NPI), which is commonly used to measure psychotic symptoms in dementia (Cummings et al., 1994). This allowed for an assessment of delusions and auditory and visual hallucinations. PPMI, on the other hand, used the Unified Parkinson's Disease Rating Scale (UPDRS) (Goetz et al., 2008), which measures psychosis using a single question that captures auditory and visual hallucinations and delusions. GENFI used a modified version of the NPI (Cummings et al., 1994), called the NPS; this scale included separate questions for visual hallucinations, auditory hallucinations, and delusions. It also included, in the options when scoring each item, an option for clinicians to enter a 0.5 or "questionable" score; for the purposes of this analysis, in order to ensure the presence of psychotic symptoms and to avoid diluting the psychotic group, these scores were set to "0" or non-psychotic for the individual item. Finally,

each schizophrenia study used a different measure. COBRE made use of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), a commonly used scale in schizophrenia research; this scale has one question for both hallucination types, but does have a separate question for delusions. FBIRN, on the other hand, uses the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984), which differentiates between the 3 symptoms. FBIRN did include some PANSS items, but not the ones related to hallucinations. The two scales additionally have a different range of responses for each item; these in addition are different from the scales in the UPDRS and NPI/NPS.

There are several important considerations here. The first has to do with item-level scaling. Each scale above includes a severity level for the symptom measured- that is, it is not just a binary presence or absence of a given symptom. This is potentially very useful and may provide rich information regarding the correlation between severity of symptoms and the measure of interest. However we encounter the difficulty that the scales are not scaled in the same manner. This difficulty can be overcome with a number of statistical techniques, such as linear or equipercentile equating (see Davier., 2003 for discussion)- though one key assumption must be met: the scales to be equated are supposed to be drawn from the *same population*. Not only are the clinical populations different in terms of clinical symptoms and age, but the way the data is collected on these populations (i.e. experience with psychosis of the clinician administering the scale; involvement of family members) is also different between groups. In addition, some of these items combine visual and auditory hallucinations- and even delusions- and others do not. As such reliable equating is unlikely to be possible in this dataset. As such, the decision was made to binarize each item- to note the ‘presence’ or ‘absence’ of a given

symptom. Next, we had to determine if the analysis would proceed on a symptom-by-symptom approach, or in terms of the binary presence or absence of psychosis. Because of the fact that some questionnaires did not allow the differentiation between symptoms- including, unfortunately, one of the schizophrenia datasets which made up a large portion of our sample size- the decision was made to also transform each patient to either having or not having psychosis, with the presence of any psychotic symptom assigning the patient to the psychotic category. We also considered creating a general disease severity variable using the Mini-Mental Status Examination in FTD and AD, and the Schizophrenia scales in Scz; unfortunately, certain data were missing from the databases which prevented completion of this variable prior to analysis.

3.3 Preparation of Dataset for Analysis and Initial Quality Control

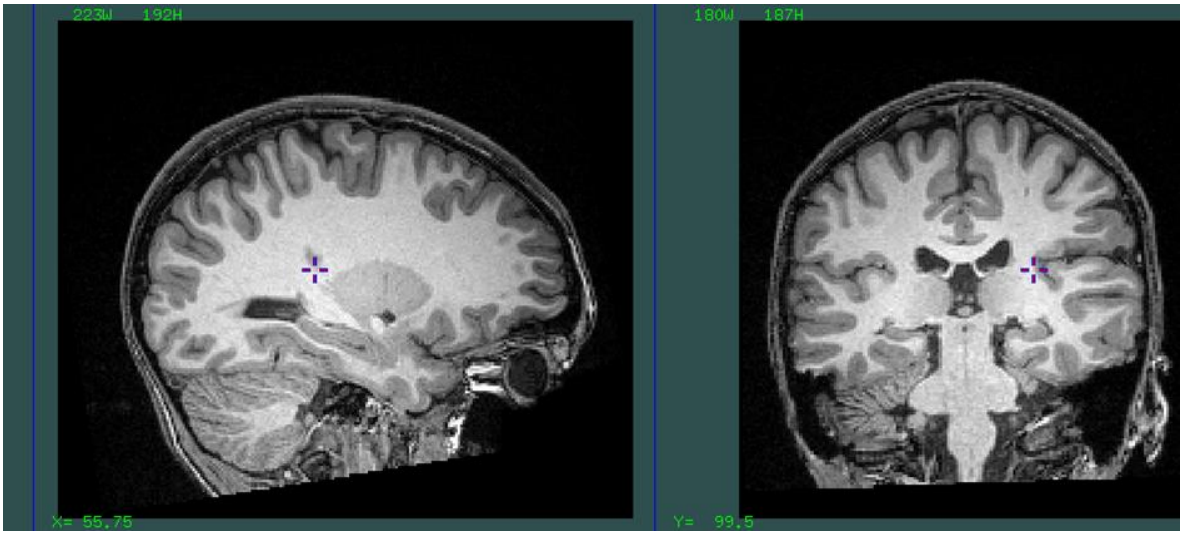
For each disorder, we divided subjects, using the binarized psychosis status described above, into a psychosis (P), disease control (DC; patients who have the disorder but who do not have psychosis) and a healthy control (HC) group. The exception to this was schizophrenia, where there was no DC group as discussed above. The value of the DC group was to assist in controlling for an important potential confound: disease-related changes that are not related to psychosis, but which may be correlated with disease severity in the same way that psychosis is for many of the disorders (see section 1.5). Within each disorder, patients were classified as having psychosis if they had auditory or visual hallucinations or delusions within one year of the scan date. This time frame was chosen to reflect a period of time within which it was reasonable to expect that structural changes in the brain would be related to the observed symptoms; while it is a challenge to estimate precisely what period of time would be reasonable, evidence from work by Fusar-Poli et al., 2011 in prodromal psychosis demonstrated that clear differences from

controls in terms of gray matter volume loss were present at baseline (i.e. during prodrome but before psychosis develops), and that the gray matter volume loss continued to worsen during the mean of two years between the baseline and follow-up scan; this suggests that noticeable changes should be present within one year of symptom onset. This was a necessary distinction to make, given that in some of the databases (e.g. PPMI) the only available scans might have been completed years before the patient, who was followed longitudinally, actually developed symptoms. It is likely that in the intervening time, as the disease progressed, other structural changes occurred which may be related to the appearance of the psychosis. For this project we included both the MCI and AD patients in the disease group, but differentiated between the two by maintaining the MCI and AD labels.

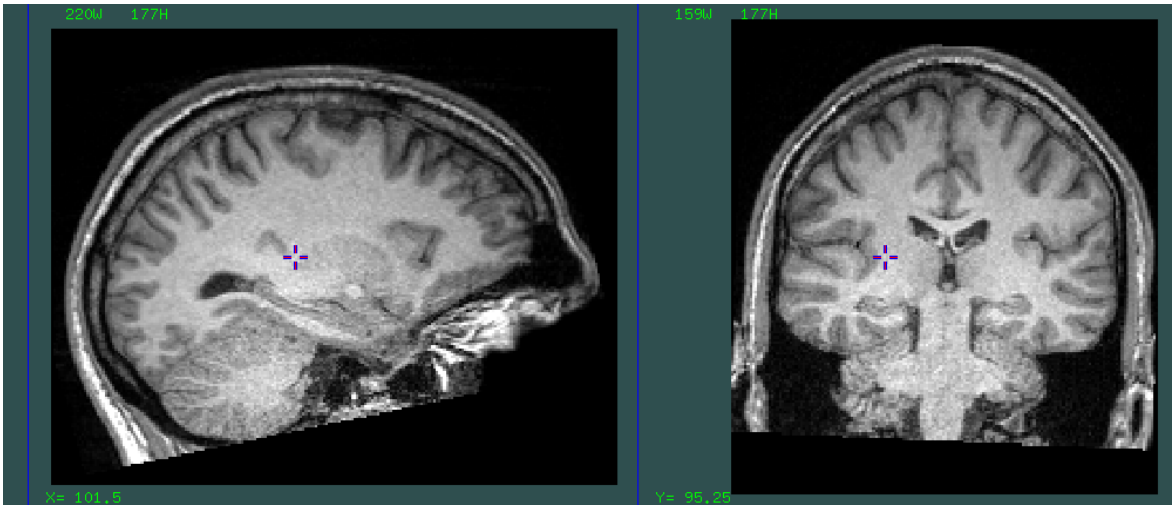
Once subjects were divided into their groups, we proceeded to ensure that no duplicates were present across groups (this could have occurred, for example, if a patient was not psychotic at one time point and became psychotic later). When a patient with psychosis had multiple scan dates, we selected the date with the most psychotic symptoms present, in an effort to maximize the signal of the underlying structural abnormalities. The psychosis groups were generally smaller, in the case of the diseases other than schizophrenia, than the control or disease control groups. This was because they represented a subset of the overall diseased group. As such, once the psychosis group was defined for each disease group, we proceeded to match them based on age and sex to healthy and disease controls. This resulted in the pre-quality control dataset which was comprised of eight groups: Scz-P, Scz-HC, AD-P, AD-DC, AD-HC, FTD-P, FTD-DC, and FTD-HC. Note that within AD patients retained their AD and MCI labels.

Once these groups were defined, we then proceeded to visual quality control using the MRI display available in the MINC toolkit. MINC is an open-source software package of tools used in imaging analysis that is built and maintained by the McConnell Brain Imaging Centre, Montreal Neurological Institute (https://bic-mni.github.io/). Images were graded in a manner adapted from Bedford et al., 2020. Images were individually assessed for their clarity and motion artefact (which are commonly encountered problems in MRI imaging (Zaitsev et al., 2015). Images were assigned a grade of 1, 1.5, 2, 2.5, 3, 3.5 or 4, based on the amount of motion perceived by the rater, e.g. ringing or blurring. Guiding images for each score (as per Bedford et al., 2020):

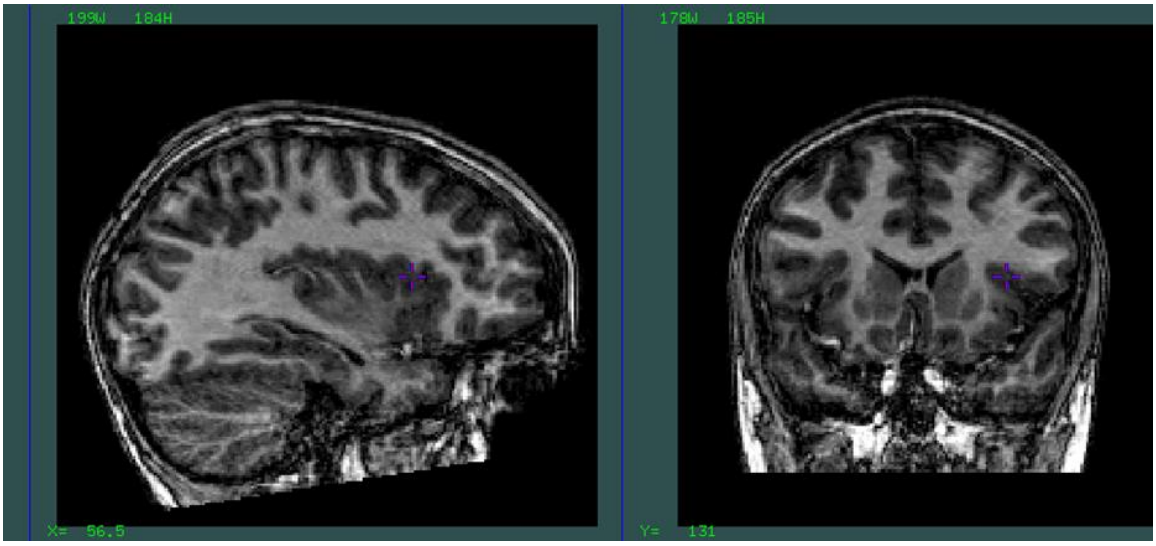
Example Score 1:



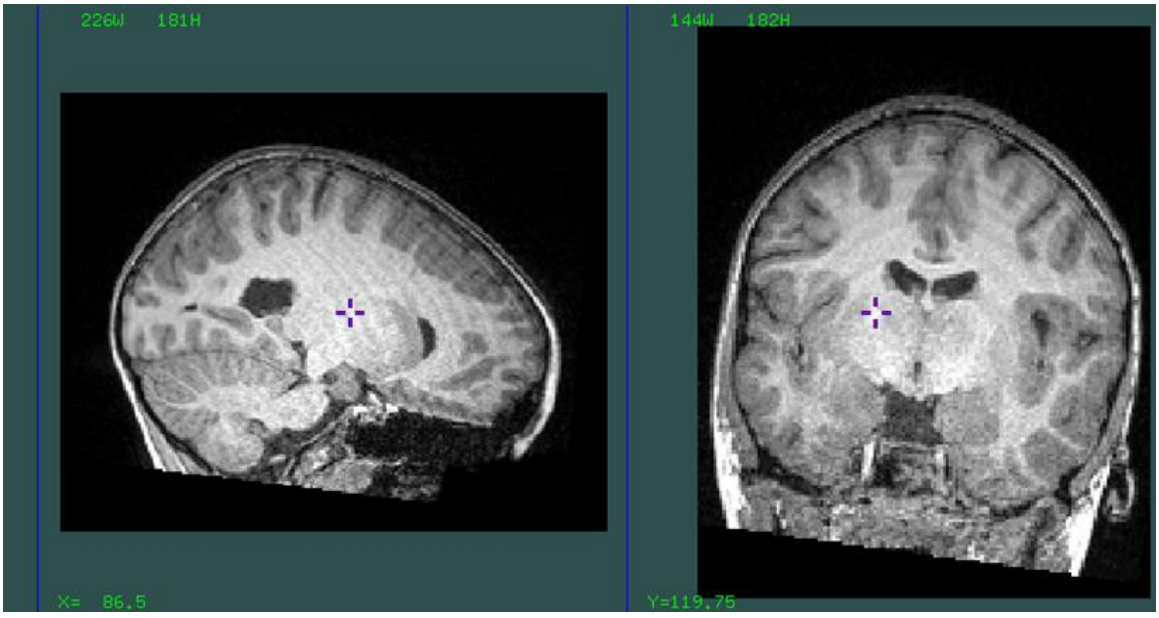
Example Score 2:



Example Score 3:



Example Score 4:



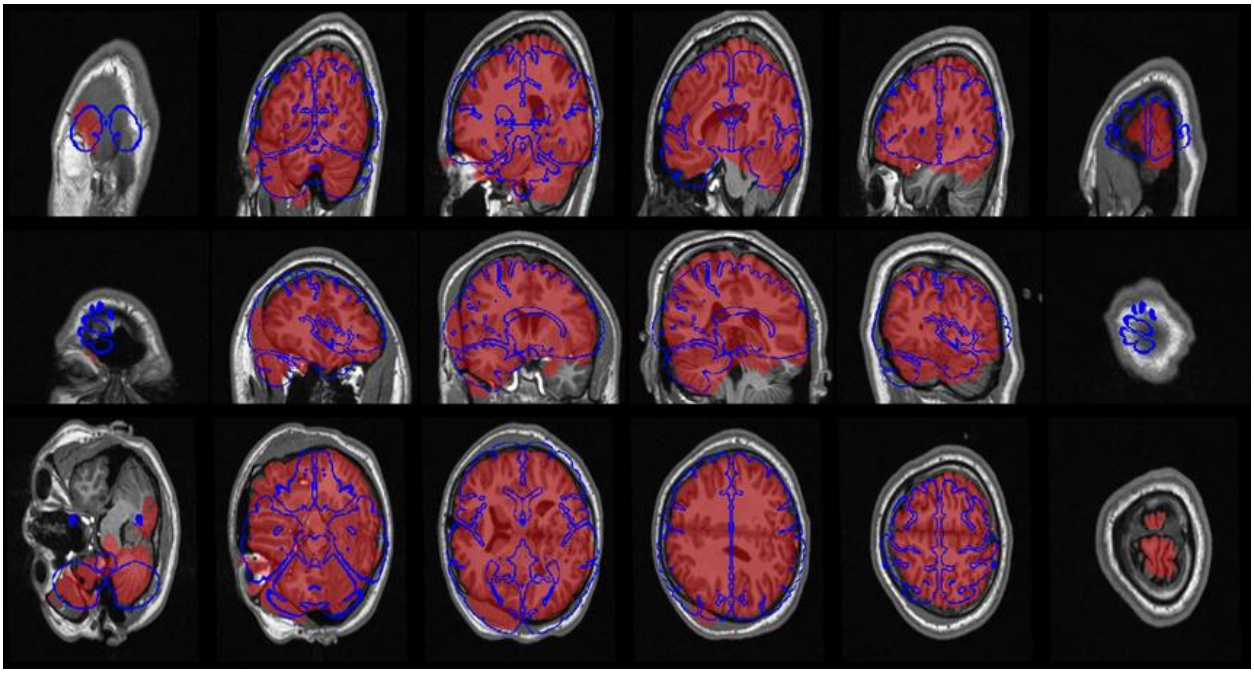
Scores of 2.5 and over resulted in the rejection of the scan due to poor quality. Whenever possible, alternative scans for the same subject close to the date of the originally examined scan were sought out and substituted in. Once visual quality control was completed, images were then ready for pre-processing.

3.4 Preprocessing

Pre-processing of images is necessary because T1-weighted structural MRI images can vary significantly between each other. For example, some may have higher or lower intensity, and images may be oriented in differing ways; these differences would render comparisons between images unreliable if they were not corrected. As such, we used the bpipe pre-processing pipeline to standardize our images prior to further processing. Bpipe is part of the MINC family of software and is available at (https://github.com/CobraLab/minc-bpipe-library). Bpipe performs bias field correction (i.e. correction of differences intensities) (Tustison et al., 2010); image registration (i.e. transforming all images to a single coordinate system (MNI space) to

allow for comparison) (Avants et al., 2008; Vincent et al., 2016); standardization of the field of view; and brain extraction using the BAaST technique (i.e. separating the image of the brain from that of surrounding tissues to facilitate analysis) (Eskilden et al., 2012). Once preprocessing was completed, images were visually inspected to ensure they had been correctly processed. Some images were found to be skewed, which was caused by the original image being excessively rotated; these images were manually rotated and run through bpipe again. An example of a bpipe output with an excessively rotated image is provided below.

Bpipe output for an excessively rotated image:



3.5 Cortical Thickness Analysis

Once preprocessing was complete we proceeded to cortical thickness analysis. This was chosen because, as noted in the introduction, grey matter deficits in a number of cortical regions characterize schizophrenia and these are also present in the other disorders under investigation.

We chose to measure cortical thickness, as reduced thickness has been shown in previous comparative studies to be a particularly important driver of reduced grey matter volume in schizophrenia (Rimol et al., 2012). We used the CIVET 2.1 pipeline provided by the BIC-MNI (http://www.bic.mni.mcgill.ca/ServicesSoftware/CIVET); this pipeline segments brain tissue into white matter, grey matter, and cerebrospinal fluid and detects the pial boundary. Then it calculates the cortical thickness by measuring the distance between the outer grey matter surface and the white matter surface interpolated onto an MNI surface template. The pipeline was run on the Niagara supercomputing cluster (Ponce et al., 2019). Once the processing was complete, each scan was examined by myself as well as an experienced rater (Elisa Guma, COBRA Lab), for quality control; scans were assigned a score of 0, 0.25, 0.5, 0.75 or 1 (with higher scores indicating better quality). Scans labeled as 0 or 0.25 were discarded; scans labeled 0.75 and 1 were included in a "high quality" scans analysis and scans labelled as 0.5 were considered as moderate quality. After an independent review of the QC by Dr. S. Ducharme, we determined that scans at 0.5 or above would be included to maximize statistical power in the dataset. QC 0.5, 0.75 or 1 were therefore included in an "all scans" analysis. We also repeated analyses keeping only the "high quality" scans to verify findings.

3.6 Subcortical Volume Analysis

Subcortical volume analysis was undertaken to assess structures, such as the striatum and hippocampus, which have been associated with the diseases being studied (see Section 2 and Discussion). For this analysis, we used the Multiple Automatically Generated Templates Brain Segmentation Algorithm (MAGeTbrain) (https://github.com/CobraLab/MAGeTbrain) pipeline (Chakravarty et al., 2013). MAGeTbrain's objective is to label different subcortical structures in

order to then be able to derive their volumes. This labelling begins with an atlas, which is manually segmented. Next, this atlas is then transformed onto a set of template images, which are 21 representative images drawn from the dataset (for this project, they were selected to be as equal as possible between the groups and representative of the groups in terms of age and sex). With these templates as a mediator, the atlas is then transformed onto the individual subject scans, with a majority vote process determining the best label for each brain region. The pipeline was four times: once for the hippocampus and its subfields using the atlas by (Winterburn et al., 2013) and once for the striatum, thalamus, and globus pallidus using the atlas by (Tullo et al., 2018); each atlas was run twice, one for the left and one for the right hemisphere. Once again, the Niagara supercomputer cluster was used to run the pipeline. While striatum, hippocampus, and thalamus have previously been implicated in schizophrenia (see section 5.1), hippocampal subfields were examined in an exploratory manner as they were provided by the atlas used.

3.7 Data Analysis and General Linear Model

Outputs of CIVET (cortical thickness measurements) and MAGeTbrain (labelled subcortical volumes) were loaded into finalized datasets and concatenated with subject ID, diagnosis, binary psychosis status, site, age and sex. These variables were all used as variables in a generalized linear model (GLM) used to predict the thicknesses and volumes. Diagnosis served to indicate whether the subject was a healthy control, or was diagnosed with Scz, AD, MCI, or FTD. Site served to help control for both differences and scanner and differences between sites in terms of protocol or procedure; as noted in Bedford et al., 2020, intersite differences and accounting for them can be critical in producing accurate and reliable results. Voxel-wise cortical thickness analyses were performed using the MATLAB SurfStat package (found at https://www.math.mcgill.ca/keith/surfstat/); the GLM was programmed into the MATLAB script

and then a contrast between the Psychosis (Positive) and Psychosis (Negative) groups were run in order to compare the two groups. Resulting comparison maps were then controlled using false discovery rate (FDR) and random field theory (RFT) for correction for multiple comparisons. In addition, an exploratory analysis was conducted using an alpha of 0.005 to check for trend-level significance in the case of lack of significance when controlling using FDR and RFT. The purpose of this is to determine regions which may be of interest in future analyses using datasets constructed with the intent of comparing between disorders. For subcortical volume, the generalized linear model functionality of SPSS (IBM SPSS Statistics 27) was used to construct the GLM and to run it for each outcome region. Age was included in the model as a covariate, and diagnosis, psychosis status, site and gender were included as factors, and each was entered to check for a main effect. Correction for multiple comparisons was accomplished via Bonferroni correction within each analysis.

4. RESULTS

My results will focus on three areas: the final datasets used in each analysis; the cortical thickness analysis; and the subcortical volume analysis.

4.1 DATASETS

The initial databases were described above. I will now describe the dataset remaining after selection of the psychotic subjects and matching them with their control groups, as well as visual quality control as described above. First it is important to note that we had to exclude the PD dataset at this point. This was because there were only 8 acceptable quality psychosis scans remaining in the PD-Psychosis group once visual quality control was completed. There were

several patients in PPMI who had good quality scans and eventually developed psychosis; however, these patients had their scans performed more than a year before their development of psychotic symptoms. As such, as the PPMI dataset was likely to have too few scans to provide a meaningful addition to the psychosis analysis, we chose to eliminate PPMI from our analysis.

Thus, 322 total patients were available for processing by the CIVET and MAGeTbrain pipelines. Of these, 149 were patients with psychosis; 125 were healthy controls; and 48 were disease controls. They were broken down by group in the following manner:

Table 1: Subgroup Characteristics prior to CIVET and MAGeTbrain processing

Group	Total N	Mean Age	Number of Female Subjects
FTD-P	25	63.8	11
FTD-DC	20	64.8	8
FTD-HC	25	62.5	10
AD-P	25	69.1	16
AD-DC	28	70	16
AD-HC	27	69.9	16
Scz-P	99	38.2	23
Scz-HC	73	38.7	24

Legend: FTD-P (FTD-Psychosis); FTD-DC (FTD-Disease Control); FTD-HC (FTD-Healthy Control); AD-P (AD-Psychosis); AD-DC (AD-Disease Control); AD-HC (AD-Healthy Control); Scz-P (Scz-Psychosis); Scz-HC (Scz-Healthy Control).

As can be seen, the majority of psychotic subjects were from the schizophrenia condition. This is not surprising, given that Schizconnect is a database aimed at providing images of

patients with a psychotic disorder. What is also apparent is the reduced proportion of female subjects in schizophrenia compared to the AD and FTD populations. These disparities do limit potential generalizability and mean that replication in other datasets with a better balance between conditions and genders would be required to confirm findings.

4.2 CORTICAL THICKNESS

We next processed the scans via CIVET. After the removal of 64 scans during further quality control, there were 258 remaining scans in the "CIVET-All Scans" dataset. Furthermore, removing 58 "borderline" quality scans resulted in a 200 scan "CIVET-Best Scans" dataset. The demographics for each dataset are presented here:

Table 2: Demographics after processing for each CIVET Condition

Condition	Total N	Mean Age (Std)	Age Range	N with psychosis	Number of females	N with Scz	N with AD	N with MCI	N with FTD	N of HC
All Scans	258	50.1 (16.29)	19-76.7	123	92	87	15	22	29	105
Best Scans	200	49.8 (16.5)	19-76.7	92	76	66	13	20	19	82

It is clear from these numbers that the quality control process had an oversized impact on patients with neurodegenerative conditions within the context of this analysis, with a large number of the patients without schizophrenia being eliminated while a large number of patients with schizophrenia remained. In addition, given that patients with schizophrenia had psychosis, of the 92-123 patients with psychosis in the final two datasets, only 26-36 of these would have

been patients with one of the neurodegenerative disorders. This pattern is repeated in the subcortical analyses and the resulting limitations will be discussed below.

In analyses using both sets of scans, no areas of cortex were found to have a statistically significant reduction in thickness between psychotic and non-psychotic subjects after correcting for repeated measures using FDR or RFT. However, in an exploratory analysis using $\alpha = 0.005$ we get the following results:

Fig. 3: CIVET-All Scans, Liberal Threshold:

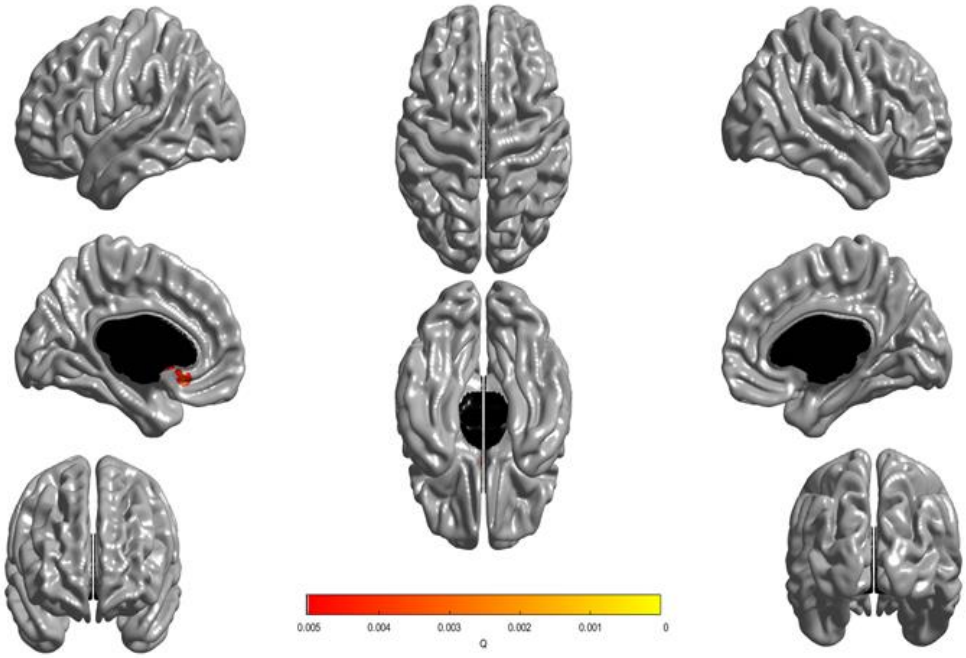
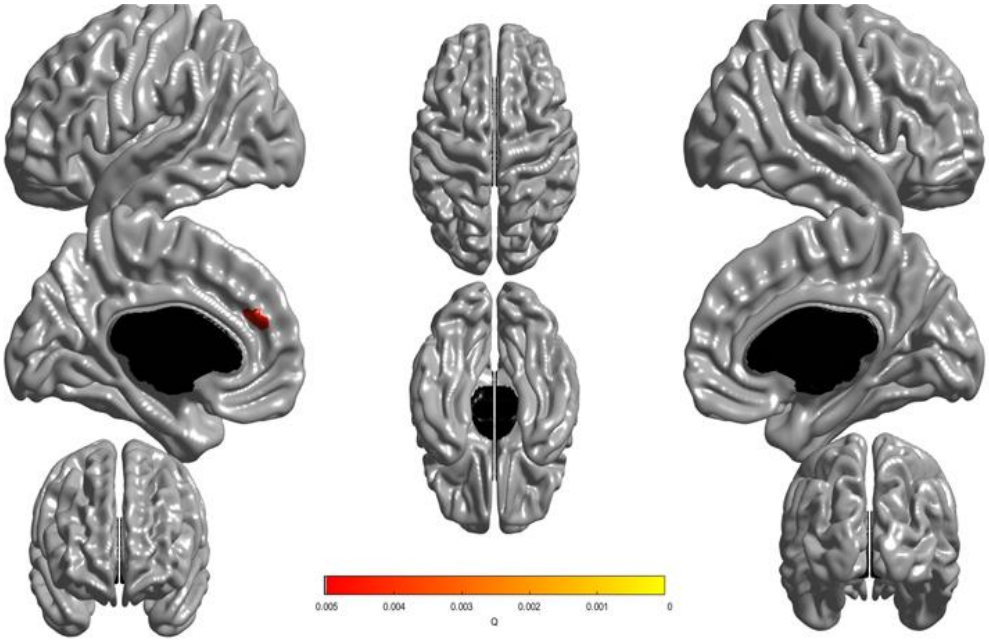


Fig. 4: CIVET-Best Scans, Liberal Threshold:



These results correspond to reduced cortical thickness in the left subgenual anterior cingulate cortex (sgACC) for psychotic compared to non-psychotic subjects in the All-Scans condition, and reduced cortical thickness in the left anterior cingulate cortex (ACC) for psychotic compared to non-psychotic subjects in the Best-Scans condition. Differences between the two conditions are a challenge to interpret- the Best-Scans condition does have higher quality scans, but also lower power given the smaller sample size. As such, for the purpose of the discussion, we will discuss the potential significance of the ACC as a region without discussion sub-regions of this structure (though it should be noted that different sub-regions of the ACC do seem to have distinctions in terms of function (see Stevens et al., 2011).

4.3 SUBCORTICAL VOLUME

The 322 scans were next run through the MAGeTbrain pipeline, in four different conditions: Hippocampus-Right, Hippocampus-Left, Subcortical-Right, and Subcortical-Left.

The pipeline failed to process a number of scans; when these were manually inspected, there was a significant overlap between these scans and those that were rejected by visual quality control after CIVET processing. The final number of scans which were processed by MAGeTbrain and which were used in each condition were as follows:

Table 3: Demographics after processing for each MAGeTbrain Condition

Condition	Total N	Mean Age (Std)	Age Range	N with psychosis	Number of females	N with schizophrenia	N with AD	N with MCI	N with FTD	N of HC
Hippocampus-Right	246	49.64 (16.29)	19-77	123	89	86	16	21	27	96
Hippocampus- Left	246	49.64 (16.29)	19-77	123	89	86	16	21	27	96
Subcortical-Right	271	50.51 (16.36)	19-77	132	96	92	17	22	31	109
Subcortical-Left	269	50.70 (16.26)	19-77	131	96	91	17	22	31	108

Given that all the patients with a diagnosis of schizophrenia had psychosis, the above data demonstrates that of the 123-132 patients with psychosis in the analyses, at most between 37-40 patients would have been patients in one of the neurodegenerative disorder groups without, whereas between 86 and 92 patients would have had schizophrenia. The limitations introduced by this are discussed below.

In the Hippocampus condition, there were five regions present in the atlas and linear regression models were generated for each; this was replicated for both hemispheres. The regions were CA1, Subiculum, CA4/Dentate Gyrus, CA2/CA3, and striatum radiatum. None of these regions had a statistically main effect of psychosis in either hemisphere; however site and gender (and for some regions, diagnosis and age) were significant covariates in a number of the models. While the specific region-by-region results for these covariates are not the focus of this thesis and as such will not be described in detail, the fact that they were significant is important from a theoretical perspective and will be discussed below.

In the Subcortical condition, the atlas provided three target regions: the striatum, the globus pallidus, and the thalamus, again for both hemispheres. Here in the left hemisphere we found a main effect of psychosis (such that patients without psychosis had larger volumes) for the striatum ($B = 758.5$; $p = 0.018$) and the thalamus ($B = 376.7$; $p = 0.018$), but not the globus pallidus ($B = 23.6$; $p = 0.70$). In the striatum model all other covariates (site, gender, age, and diagnosis) were statistically significantly related to volume; for the thalamus, this was true for all covariates except site. In the right hemisphere, we observed a similar pattern, with a main effect of psychosis for the striatum ($B = 759.1$; $p = 0.014$) and the thalamus ($B = 359.6$; $p = 0.026$), but not the globus pallidus ($B = 45.7$; $p = 0.40$). All other covariates also had main effects in the striatum and all covariates other than site had a main effect in the thalamus. When applying a strict Bonferroni correction within each dataset (corrected alpha = 0.0167), only the right striatum ($p=0.014$) survives correction for multiple comparisons; however, both the left thalamus and left striatum are trending towards significance. As such, for purposes of discussion and in light of the other limitations which will be discussed below, I will discuss the potential

significance of both striatum and thalamus. In addition, it is relevant to note that again the chosen covariates have demonstrated significant main effects; this is important not only because it demonstrates that these were relevant covariates to include, but because it allows us to make important general points about future imaging work in this field.

5. DISCUSSION

In this manuscript, I have described an approach to trans-diagnostic imaging in psychosis. The main hypothesis is that, by looking at structural MRI images across the three conditions- AD, FTD and schizophrenia- we would be able to demonstrate which structures are most affected in psychotic vs. nonpsychotic individuals; this in turn would help us identify which structures are most likely to be related to psychosis as opposed to the underlying disease. The purpose of this, in turn, is to help identify the brain regions most likely to be involved in a 'final common network' underlying psychosis. This in turn would help to better focus therapeutics and prevention research in the future by providing more psychosis-specific targets for intervention. Here we will discuss the obtained results and their implications and relation to other work, as well as the limitations of this work and what these limitations may have to teach us about the design of future trans-diagnostic neuroimaging efforts. In addition, we will discuss the results obtained in this study from a computational lens, with a view to beginning to generate hypotheses of how these results may help improve our mechanistic understanding of psychosis.

It should be noted, given the interest of this work in identifying a final common network, that functional imaging, such as fMRI, would have been an ideal complementary method to this

structural analysis. While this is an excellent direction for future research, this was not pursued during the current study for two reasons. The first is that fMRI images were only available for a subset of patients in the available databases (patients in ADNI 1 did not have fMRI), and for this first analysis we chose to maximize the sample size. The second is that the results from this analysis will help to define hypotheses for future analyses of functional data.

5.1 Cortical and Subcortical Results

We begin with a discussion of the cortical thickness results. As noted above, when correcting for multiple comparisons with FDR or RFT, both commonly used methods in neuroimaging (Worsley, 1996; Genovese et al., 2002), no regions were significantly different between psychotic and nonpsychotic subjects. This result is initially surprising; as discussed in the literature review, a number of regions of grey matter reduction have been noted when comparing patients with schizophrenia to healthy controls. When considering the final numbers of patients in the analysis after quality control, a potential explanation may be that the scans of psychotic non-schizophrenic patients were not present in sufficient numbers to generate consistent between-condition differences, while at the same time the mixing of healthy controls and patients with disease in the nonpsychotic group introduced grey matter deficits which reduced the separation from the psychotic group. In addition, it is relevant to note that the main psychotic sample, because of quality control, came from schizophrenia patients, who were much younger than the healthy controls from the other conditions; as such, the psychotic group of mostly schizophrenia patients was being compared to an older control group (mean age of the psychotic sample in the all-scans analysis: 45.9 (Std. 16.9); mean age of the nonpsychotic sample

53.8 (Std. 14.8); significantly different with a t-test, t=3.98, df=256, p = 0.000). As such, despite initial efforts to age-match each group within-dataset, after post-CIVET quality control the analysis was not being performed between aged-matched groups. This is another potential reason for the minimization of differences between the psychotic and nonpsychotic groups- because the patients with psychosis may have had grey matter reductions which would have been more apparent compared to age-matched controls. This occurred in the context of a trans-diagnostic study, where differential elimination of scans from the different databases involved occurred in a manner that would have had less of a chance of occurring when looking within-disease or within-database and led to the loss of age matching and also a reduction of balance of scans between-condition. Further discussion of this result can be found below where I discuss study limitations and what they may teach us about design of future studies.

When using a more liberal correction for multiple comparisons, we do find significance for regions corresponding to the dorsal and subgenual anterior cingulate cortices, with both regions having a reduced thickness in psychotic compared to non-psychotic subjects. While this result can only be considered exploratory, the fact that it is the only cortical region that becomes significant when the significance threshold is lowered may increase our confidence that it is a potentially significant result. Had many regions become significant when the threshold was lowered, it would have been more challenging to determine which regions are worth further exploration and which are more likely to be spurious. The ACC itself is an extremely important region in a number of networks and disorders (Drevets et al., 2009; Stevens et al., 2011), and it has been implicated in psychosis, with grey matter reductions in the ACC potentially preceding psychosis onset (Fornito et al., 2009). As such, this finding is in line with previous research in

psychosis and further exploration of this region in ROI analyses in future trans-diagnostic work is likely to be warranted. The computational implications of reduced ACC thickness as well as what this may mean in the context of the subcortical results is further discussed below.

The results for subcortical volume include findings of bilateral reductions in thalamic and striatal volume in psychotic subjects. There were no significant findings in the hippocampus. Given the reductions in hippocampal volume noted in schizophrenia (see Lieberman et al., 2018, for a review), this is initially surprising. However, the same limitations discussed above in the cortical thickness analysis may be at play here, as may be the fact that the disease control patients are likely to have had hippocampal reductions. Another interpretation of this result is that the reduction in hippocampal volume may be related more to the underlying disease than to the presence of psychotic symptoms. We will discuss the potential computational implications of this below. The finding of reduced striatal volume is intriguing given the sample of psychotic patients was mostly comprised of patients with schizophrenia. This is because previous literature has noted that patients with schizophrenia who were medicated or previously medicated had larger striatums, whereas patients who had not been medicated had smaller striatums (Shihabuddin et al., 1998; Ballmaier et al., 2008; Keshavan et al., 1998; discussion in Koch et al., 2018); this indicates that the ‘default’ deficit in schizophrenia is indeed a smaller striatums. While information about medication status was not present in our dataset, it is unlikely that the majority of these patients were antipsychotic naive. However, a more recent study, Kock et al., 2018, found decreased volume of the putamen in even medicated patients compared to control subjects, and no correlation between chlorpromazine-equivalent dosage of antipsychotic and putamen size in their sample. As such, as Koch et al. suggest, the literature on striatal volume in

schizophrenia is mixed, but evidence for lower volumes, even in medicated patients, does exist. This finding may have potentially important computational implications in terms of our understanding of the mechanisms underlying psychosis and the potential importance of dysfunction of the dopaminergic system as one point of failure that could lead to psychotic symptoms across conditions. Finally, the finding of thalamic volume reduction is interesting for a number of reasons. The thalamus is a key region for the relaying of both sensory information (Torrico et al., 2020) and is of course part of cortico-striatal-thalamo-cortico loops which may have important implications for the mechanisms underlying psychosis (Peters et al., 2016). In addition, there is a previous literature on thalamic involvement in schizophrenia, with thalamic deficits hypothesized as leading to impairments in the coordination of perception and the encoding and retrieval of information (Andreasen, 1997).

5.2 Potential Computational Significance and Psychosis as a Failure State

The purpose of this project was to identify regions that are specific to psychosis, regardless of the underlying disease. Given that there is often a prodromal state in schizophrenia prior to the onset of frank psychotic symptoms (see Larson et al., 2010, for a review) and given that, as discussed in the introduction, psychosis is generally a feature of more severe AD and FTD, we can argue that psychosis represents a state which obtains after a number of structural and functional alterations occur (Chung et al., 2016). The fact that similar symptoms (though not in the same proportions, which will be discussed below) can occur in all three disorders then raises the possibility that psychosis is in fact a ‘failure state’ that the brain as a system can find itself attracted to, given the appearance of a number of possible deficits or chains of deficits. This

concept of psychosis as an attractor state has been previously discussed (see Adams et al., 2013), though here we suggest that this concept can be extended trans-diagnostically. This proposition provides part of the rationale as to why we might discover regions which have similar dysfunction across the three conditions studies. It is important to note, however, that the cross-sectional nature of this study (and limitations of the databases examined) does not allow for a definitive account of the sequence of cortical or subcortical dysfunctions in each disorder which lead to the development of psychotic symptoms. That being said, the finding of some regions which are common to the three disorders in psychosis does allow, in the context of previous work, for the generation of some hypotheses which could be explored by better designed datasets in the future.

We will focus this discussion on the potential computational roles of three regions relevant to our results: the ACC, striatum, and thalamus. The ACC has increasingly been recognized as having computational importance in a number of psychiatric conditions, such as depression (Ramirez-Mahaluf et al., 2017). In this account, it is seen as mediating between cognitive and affective processing, helping to switch between the two. Indeed, the ACC is seen as a mediator between various brain functions in situations where they may conflict, and it has also been implicated in the reward and action selection pathway, receiving input from the ventral striatum through a circuit that involves a thalamic relay (Haber, 2011). In order to interpret the potential computational significance of the results we obtained regarding these regions, it is helpful to adopt a theoretical framework which can assist in providing a unified account.

In previous work (Benrimoh et al., 2018 and Benrimoh et al., 2019) I laid out a model of auditory verbal hallucinations; in more recent, in press work, (Adams et al., 2021) laid out a model with similar properties which underlies delusions. These models were created using the Active Inference framework (Friston et al., 2017). It should be clear at the outset that this is not the only theoretical framework for hallucinations; it is chosen for the purpose of scaffolding this discussion and because it has a history of *in vivo* neurobiological validation of its computational parameters (see Benrimoh et al., 2018, for a discussion). While a full discussion of the theoretical and mathematical foundations of Active Inference are beyond the scope of the current work (see Friston et al., 2017, for further discussion and see Benrimoh et al., 2021, for a clinically intuitive definition), we will review the key principles here. Active Inference is a Bayesian theory of the function of self-organizing systems, such as the brain, which posits that their basic function is to reduce their uncertainty in their models of the world. This uncertainty is reduced by observing data (observations), comparing it to prior information (priors), and then generating updated (posterior) beliefs. What is key under Active Inference is that agents are not simply passive observers; they can *act* in order to gain new information (exploration) or to place themselves in sensory states which suit their priors (exploitation). Agents do not have direct access to the external world and therefore must infer the causes of their sensations; their models of the world allow them to predict the expected sensory outcomes (and potential to reduce uncertainty) of certain actions, which aids in action selection. Under Active Inference the actions or sequence of actions one takes is called a *policy*; the set of actions available are referred to as a *policy space* (Benrimoh et al., 2018). Policies are important because they not only lead to changes in available information, but they also *engender expectations about the sensory states they will produce.* This is necessary because *policies are chosen as a function of their expected*

reduction in uncertainty. The final quantity that must be understood is *precision*. This is a parameter that measures the confidence placed in a particular source of information, the attention afforded to a source of information, or alternatively its clarity and integrity. For example, in a dark room very little confidence or precision is afforded to visual information, as it barely exists, and relatively more precision is afforded to auditory information.

In the previous work on hallucinations noted above (Benrimoh et al., 2018 and 2019), the basic account of this psychotic symptom in Active Inference terms is as follows: hallucinations occur when a maladaptive but strongly held prior belief can no longer be corrected with high-precision sensory evidence. In this case, the priors are derived from policies which involve listening to another agent in the world. When the agent chooses to listen, it expects a voice to be present. In a normal situation, the agent would be able to use its sensory information (i.e. hearing nothing) to correct its perception- despite the prior expectation of a voice, the high precision of information in the auditory domain allows for the formation of the correct posterior percept, which is that no sound is present. This in turn allows the agent to select a more appropriate policy for the future that better fits the world it is existing in. However, if that policy choice is made less flexible- by reducing the number of available policies or increasing the prior precision of those policies (which is simulated by increasing a parameter called 'gamma' which represents elevated midbrain dopamine (Schwartenbeck et al., 2015))- and the sensory precision is lowered below a certain threshold, suddenly the brain is no longer able to use sensory information to arrive at the correct percept and the prior belief that a voice should be present prevails, resulting in a hallucination. This 'precise prior, imprecise evidence' model was also later used to simulate prodromal states, thought disorder, and hallucinations divorced from current context, and a

recent extended model has demonstrated the importance of mood in the shaping of delusional content, of affect in the precipitation of delusions, and of the balance between priors and sensory precision in the generation of delusional states (Adams et al., 2021). In addition, experimental work has demonstrated the importance of priors in driving hallucinations (Vercammen et al., 2010; Teufel et al., 2015). Given the importance of priors derived from selected policies, when a hypothetical map of potentially implicated brain regions was constructed, one key region involved in the policy selection step was the striatum (Benrimoh et al., 2018), given its role in action selection (Kimchi et al., 2009; Bariselli et al., 2019). However, initially no specific role for thalamus or the ACC was hypothesized.

Using the Active Inference framework, we can try to interpret the observed results in this paper and generate new hypotheses. To begin, as noted the striatum was always postulated to have a role given its importance in action/policy selection. This is related to, but importantly *not* identical with, the importance of dopamine signaling in the striatum. As discussed, *either* the restriction of the policy space *or* the increase in prior precision over policies (i.e. dopamine signaling) was related to hallucination onset in the Active Inference models. As such, the finding of reduced striatal volume in the psychotic group, though it does not directly provide evidence regarding dopamine signaling, does allow us to hypothesize that it may be a marker of reduced policy space or at least reduced efficiency in the selection between policies. This likely occurs in tandem with cortical thickness reductions, as cortex is also involved in the policy (action) selection and evaluation process (Seo et al., 2012), but the particular regions of cortex affected may vary based on condition, and this may in turn have an effect on the content or modality of the hallucination or the content of the delusion. In this conceptualization, important elements of

the priors, located in cortex, may vary between disorders, but the common point of failure is the striatum, where policy selection becomes less flexible, resulting in the generation of the maladaptive priors which, in the presence of degraded sensory precision, leads to hallucinations or delusions. For example, the hippocampus, which is affected in AD, schizophrenia and, with a different pattern, in FTD (Laakso et al., 2000), but which is not in our analysis specific to psychosis, may serve as a source of maladaptive priors; these priors on their own do not lead to psychosis, however, unless further dysfunction in striatal action selection and reduction in sensory precision occurs. The reduction in sensory precision itself could be related to reductions in attention-related acetylcholine signaling, common in both AD and schizophrenia, or reductions in white or gray matter integrity, which can be found in all three disorders (but in varying patterns which, again, may lead to the differing psychotic phenotypes between the three disorders).

Roles for both the ACC and the thalamus in our computational model can also be derived. The ACC is involved in the flexible mediation between different brain regions and the priors and policies they represent; a failure in this region, as simulated by (Ramirez-Mahaluf et al., 2017) in depression, leads to less effective switching between computational strategies. This would assist in the generation of a less flexible, maladaptive policy space. The ACC is critical in evaluating the outcome of actions (Jahn et al., 2014); weakening of thalamic input to the ACC would further reduce its ability to help select appropriate actions or produce a more adaptive policy space. As such, the findings in this study partially cohere with the existing Active Inference model while providing useful potential additions to it. These additions, in turn, could be tested in future experiments. For example, tasks currently in development which measure

policy space or the flexibility of policy selection (see Benrimoh et al., 2021 for further discussion) could be correlated with structural covariance between the ACC, striatum and thalamus, and functional imaging could be used to provide another source of evidence via the examination of functional connectivity between these regions and its correlation with the tasks. In addition, pharmacological manipulations that reduce acetylcholine (such as scopolamine), as a proxy for sensory precision, could be used to test the hypothesis that subjects with either reduced integrity of these three regions or reduced functional connectivity between them would be more likely to hallucinate or experience delusions than subjects where these regions or their connectivity are relatively preserved.

Should the interplay between these three regions be validated as being mechanistically related to the onset of psychosis, another relevant step would be to engage in longitudinal imaging projects aiming at determining the order in which these regions become dysfunctional compared to other brain regions in each disorder in order to confirm their status as being part of a 'failure mode' leading to psychotic symptoms. This could theoretically have implications for new approaches to treatment. Firstly, it would provide new targets for intervention. As noted, at present the mainstay of treatment is antipsychotic medication which essentially targets dopaminergic signalling in the meso-limbic pathway. A better understanding of the wider circuits involved may allow for the targeting of rTMS or deep brain stimulation interventions, as has been demonstrated in depression (Berlim et al., 2013; Mayberg et al., 2005), and which may be applicable across disorders- providing a useful intervention applicable to a wide range of patients. In addition, novel therapies- for example, pro-cholinergic therapies which have recently

demonstrated effectiveness in schizophrenia (Brannan et al., 2021)- may be utilized in order to delay or head off the development of psychotic symptoms.

5.3 Limitations and Implications for Future Transdiagnostic Study Design

As suggested in preceding sections, this study has a number of important limitations. One already discussed was the large and biased reduction in available scans once quality control was put into place. Quality control of images is extremely important and has recently gained more recognition as being a necessary step to improve reliability of results (Ducharme et al., 2016). Quality control at multiple steps is also important in that it helps ensure that poor quality scans do not propagate errors throughout multiple phases of an image processing pipeline. When performing an analysis between two defined groups within the same databases, loss of images due to quality control is a negative mostly with respect to the reduction in the power available to detect significant differences. However, when dealing with multiple databases and disorders, a different problem arises- that of biased or differential image loss. Poor image quality is often due to motion artefact and it can result in inaccurate results, such as apparent cortical thinning which is in reality due to blurring of the grey-white matter boundary by the motion (Alexander-Bloch et al., 2016) and it is the case that the more ill a subject is, the more likely they are to move while in the scanner. This in turn means that healthy controls are less likely to be eliminated during quality control, and more globally ill patients are more likely to be eliminated. In our case, this led to a significant reduction in the number of patients with AD or FTD and psychosis, and to the complete elimination of the PPMI dataset. This in turn led to an exacerbation of the imbalance in sample sizes between groups within the psychotic group and likely reduced the number of

significant findings. Some solutions to this problem do exist, and can be divided into solutions employed during scan acquisition and those employed after scan acquisition. Some studies in children and adults have demonstrated that audiovisual stimuli deployed in the scanner may help reduce motion artefact, though these have yet to be tested in patients with cognitive impairment or other behavioral issues, and could interfere with task-based functional imaging protocols (Greene et al., 2018; Powell et al., 2015). In the realm of solutions employed after scan collection are techniques for the correction of motion during image processing, potentially using motion tracking data collected during a scan (Havsteen et al., 2017).

While not a limitation per se, it is also relevant to discuss some of the covariates which were controlled for in this study. It is important to note that site and age were both significant covariates. Controlling for age was crucial, given the age difference in the final analyzed psychotic vs. nonpsychotic sample discussed above, and will remain an important consideration in future transdiagnostic studies where age of illness onset is fundamentally different between diseases. Site (here an amalgamation of both inter-site and inter-scanner differences) is also important to control for. As discussed in (Yamashita et al., 2019), differences between sites can be an important source of variance which could drive spurious results when investing psychiatric disorders; meta-analytic approaches to this (e.g. Bedford et al. 2020), may be optimal, and should be considered in future transdiagnostic studies.

As discussed previously, we were not able to disentangle visual and auditory hallucinations for certain subjects because of how these were captured, and because of concerns regarding the sample size for each individual psychotic symptom (as well as their co-occurrence

in many patients). This leads to the limitation that we were considering ‘psychosis’ as a phenotype and ignoring distinctions between individual psychotic symptoms, despite the fact that the incidence of specific psychotic symptoms varies between diagnoses as discussed previously. While we provide a rationale for examining psychosis as a phenotype defined as a disconnection from reality regardless of the modality, it remains possible that certain brain regions more related to a particular symptom rather than the phenotype as a whole were missed in this analysis. In addition, in this analysis, as we were considering structural changes, we allowed psychotic symptoms to have occured within one year of the scandate. However psychosis can be a ‘state’ rather than a ‘trait’ and clinically symptoms can fluctuate depending on patient treatment and metabolic or infectious stressors; in addition, it is possible that structural changes not related to psychosis could have occurred in the given time delay. Future studies which make a point of scanning patients when symptoms are or have recently been present, as well as studies which employ functional imaging to detect state signals may help to counteract these limitations.

Another important limitation to consider is the potential of collider bias. Collider bias occurs when an exposure and putative outcome are actually caused by a third variable; when that variable is controlled for, it can lead to a spurious association between the exposure and the outcome (Lee et al., 2019). In our case, the bias might manifest in the following way: within the psychosis group, all patients have some disease. As such, it is possible that any correlation between cortical thickness or subcortical volume and psychosis are actually caused by having a disease rather than the psychosis. An important part of the design of our study was to include disease controls- patients without psychosis but with a neurodegenerative disease- in order to supplement the healthy controls and reduce the risk of collider bias by having a more diverse

comparison group. There were limitations to this, such as the absence of a disease control group for schizophrenia, and the presence of patients with MCI in the AD database (MCI patients are less likely to have psychosis as they are at an earlier illness phase and as such are more likely to be in the disease control group while also serving as a less optimal disease control for AD given their less severe illness). Future studies aimed at transdiagnostic studies of neuropsychiatric symptoms should continue to include disease controls in order to help reduce the risk of collider bias.

During dataset preparation, a number of issues were encountered when working to combine datasets together. Firstly, different databases used different imaging formats (e.g. .nii as opposed to .mnc) which needed to be transformed into a common format and at times rotated in order to be placed in the same pipeline. This introduces the risk for human error and for variations which could impact on processing pipelines. For example, the .mnc format provided in the ADNI database had an error that caused a later pipeline to fail, leading to the need to re-download the ADNI images in .nii format and transform them to .mnc format using a command that was part of the MINC toolkit. Errors in programming at every step of this process could induce new errors which could be minimized by the use of a universal imaging format. Databases also at times included both 3T and 1.5T images, and these were not always clearly labeled. This in turn can lead to comparison of images of varying quality. Finally, the different databases, having been designed for experiments with different purposes, included different demographic features and measures of neuropsychiatric symptoms, as well as different measures of disease severity (even within disease), which in turn leads to a reduced ability to control for demographic measures and disease severity across datasets, or to ask questions relating to

mediating or moderating factors. Future large-scale image collecting consortia could align on a basic equivalent set of demographic and neuropsychiatric data to facilitate database integration and comparison.

These limitations provide us with a set of recommendations which could be made for future trans-diagnostic work.

1. Large data collection projects should align on a common set of measures for demographic and neuropsychiatric instruments, similar to the recommendations being put forward by the NIMH for common data elements to be collected as part of psychiatric research (NIMH notice NOT-MH-20-067).
2. These projects should also align on common image formats, and to organize this and related data into a common format (such as the BIDS (https://bids.neuroimaging.io/) format).
3. Imaging projects hoping to probe neural correlates of specific neuropsychiatric symptoms or symptom clusters should include, whenever possible, significant numbers of valid disease controls to help reduce collider bias
4. Imaging projects should align on and implement rigorously a set of best practices for the minimization of motion artefact.

6. SUMMARY AND FUTURE WORK

This work is, to our knowledge, the first to compare Schizophrenia to a number of other neurodegenerative disorders, with the goal of determining the changes in brain regions most specific to the psychosis phenotype itself, as opposed to the underlying disease. As discussed, the

main finding is that striatal and thalamic volumes are reduced in patients with psychosis and schizophrenia, AD or FTD compared to nonpsychotic healthy or disease controls. An exploratory analysis also revealed a reduction in the thickness of the ACC. These results have the potential to expand existing computational models by highlighting the importance of ACC and striatal policy selection as well as thalamic inputs into this process, which in turn creates an opportunity for novel therapeutics research should these results be replicated and their computational significance be confirmed by future experiments. Future work will also focus on other imaging modalities and analyses, such as fMRI or structural covariance, to further probe and validate these results. Finally, a set of recommendations for future transdiagnostic imaging initiatives is provided which may help avoid some of the limitations found in this study in future work.

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