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Altered tract-specific white matter microstructure is related to poorer cognitive performance: The Rotterdam Study

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ABSTRACT

White matter microstructural integrity has been related to cognition. Yet, the potential role of specific white matter tracts on top of a global white matter effect remains unclear, especially when considering specific cognitive domains. Therefore, we determined the tract-specific effect of white matter microstructure on global cognition and specific cognitive domains. In 4400 nondemented and stroke-free participants (mean age 63.7 years, 55.5% women), we obtained diffusion magnetic resonance imaging parameters (fractional anisotropy and mean diffusivity) in 14 white matter tracts using probabilistic tractography and assessed cognitive performance with a cognitive test battery. Tract-specific white matter microstructure in all supratentorial tracts was associated with poorer global cognition. Lower fractional anisotropy in association tracts, primarily the inferior fronto-occipital fasciculus, and higher mean diffusivity in projection tracts, in particular the posterior thalamic radiation, most strongly related to poorer cognition. Altered white matter microstructure related to poorer information processing speed, executive functioning, and motor speed, but not to memory. Tract-specific microstructural changes may aid in better understanding the mechanism of cognitive impairment and neurodegenerative diseases.

1. Introduction

Brain white matter damage is increasingly recognized as an important factor in the pathophysiology of cognitive impairment and dementia (Brun and Englund, 1986; Pievani et al., 2010; Sexton et al., 2011; Wang et al., 2012). Evidence shows that macrostructural white matter changes, such as white matter lesions, white matter atrophy, and lacunes, relate to poorer cognitive performance. Studies have already suggested a regional pattern of association between these macrostructural white matter changes and specific cognitive domains (Benjamin et al., 2014; Smith et al., 2014; Vernooij et al., 2009). At the same time, it is thought that such conventional markers only represent the tip of the iceberg of white matter changes. Focusing on microstructural changes by means of the microstructural integrity of the white matter may provide a more in-depth insight of alterations in the white matter. Perhaps more importantly, the white matter is not a bulk substance but consists of different white matter tracts, which are important for the connection of different cortical regions (Doricchi et al., 2008). Changes in white matter microstructural integrity are accompanied by changes in diffusion magnetic resonance imaging (MRI) parameters. Fractional anisotropy (FA) is generally lower and mean diffusivity (MD) is generally higher (with exceptions) in older or diseased brains, which is thought to reflect reduced white matter microstructure (Beaulieu, 2002; Maclullich et al., 2009).

Altered microstructure of white matter tracts, for example, as a result of aging or pathologic processes, is presumed to lead to loss of communication between cortical regions, resulting in poorer cognitive performance, the so-called “disconnection hypothesis” (Nazeri et al., 2015; O’Sullivan et al., 2001; Salat et al., 2005; Teipel et al., 2014; Vernooij et al., 2009). Information processing speed and executive function are the most consistently impaired cognitive functions that have been related to white matter damage (Santiago et al., 2015; Tuladhar et al., 2015; Zhang et al., 2015). However, the potential role of specific white matter tracts on top of a global white matter effect in cognitive performance remains unclear, especially when considering specific cognitive domains. It is necessary to investigate these potential roles for specific white matter tracts to

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elucidate probable mechanism of cognitive impairment and neurodegenerative diseases. Therefore, the purpose of this study was to determine the tract-specific effect of white matter microstructure on global cognition and specific cognitive domains in a large, middle aged, and elderly population of 4400 persons from the population-based Rotterdam Study (Hofman et al., 2015), using diffusion MRI.

2. Materials and methods

2.1. Study population

This study is based on participants from the Rotterdam Study, an ongoing, prospective, population-based cohort study including participants of 45 years and older living in Ommoord, a suburb of Rotterdam (Hofman et al., 2015). From 2005 onward, MRI scanning was included in the study protocol (Ikram et al., 2011). Between 2006 and 2011, 5430 nondemented participants without contraindications for MRI (including claustrophobia) were eligible for scanning. Among these persons, 4841 underwent a multisequence MRI acquisition of the brain, including diffusion-weighted MRI scanning. We excluded scans with incomplete acquisitions ($n = 53$), scans with artifacts hampering automated processing ($n = 112$), and scans with MRI-defined cortical infarcts ($n = 160$). We additionally excluded 116 participants with history of clinical stroke. This resulted in 4400 individuals with analyzable MRI data. Of these, 3876 participants had fully available cognition data. MRI scanning and cognitive assessment took place at the same visit, apart from 677 participants who underwent MRI scanning on average 1.9 years (standard deviation [SD] 0.6) before cognitive assessment.

The Rotterdam Study has been approved by the medical ethics committee according to the Population Study Act Rotterdam Study, executed by the Ministry of Health, Welfare and Sports of the Netherlands. All participants gave written informed consent.

2.2. MRI acquisition and processing

We performed multisequence MRI on a 1.5-T MRI scanner (GE Signa Excite), undergoing a quality assurance protocol keeping the system unchanged (no major updates or upgrades) for the period of inclusion. The imaging protocol was described extensively elsewhere (Ikram et al., 2011). Because of a technical problem between February 2007 and May 2008, 1312 subjects were scanned with the phase and frequency encoding directions swapped for the diffusion acquisition, which led to a mild ghosting artifact in the phase encoding direction (de Groot et al., 2015). This was treated as a potential confounder in the analysis (see Section 2.7).

An automated tissue segmentation approach was used to classify scans into gray matter, white matter, cerebrospinal fluid (CSF), and background tissue. Intracranial volume (ICV) (excluding the cerebellum and surrounding CSF) was estimated by summing total gray and white matter and CSF volumes and used to correct for head size (Vrooman et al., 2007).

White matter lesions (WMLs) were identified using an automated postprocessing step based on the fluid-attenuated inversion recovery image and the tissue segmentation (de Boer et al., 2009). We visually assessed the presence of infarcts on structural MRI sequences, and in case of involvement of cortical gray matter, we classified them as cortical infarcts.

2.3. Diffusion-MRI processing and tractography

For diffusion MRI, we performed a single shot, diffusion-weighted spin echo echo-planar imaging sequence. Maximum b value was 1000 seconds/mm^2 in 25 noncollinear directions; 3 volumes were acquired without diffusion weighting (b value = 0 second/mm^2). All diffusion data were preprocessed using a standardized pipeline (Koppelmans et al., 2014). In short, eddy current and head-motion correction were performed on the diffusion data. The resampled data were used to fit diffusion tensors, allowing (in combination with the tissue segmentation) computation of global mean FA and MD in the normal-appearing white matter.

The diffusion data were also used to segment white matter tracts using a diffusion tractography approach described previously (de Groot et al., 2015). For 14 different white matter tracts (11 of which segmented bilaterally), tract-specific white matter microstructural diffusion-MRI parameters (median FA and MD) were obtained with subsequent combination of left and right measures (Fig. 1) (de Groot et al., 2015). The average reproducibility of our tract-specific measurements was 87%, which is good (de Groot et al., 2015). We standardized tract-specific diffusion-MRI parameters (0 mean and unit SD) to facilitate comparison of associations. Tracts were categorized, based on anatomy, into brainstem tracts, projection tracts, association tracts, limbic system tracts, and callosal tracts (de Groot et al., 2015).

Tract segmentations were also used to acquire tract-specific white matter volumes and by combining the tissue and tract segmentation tract-specific WML volumes. Tract-specific WML volumes were natural-log transformed, to account for their skewed distribution.

The cerebellum could not be fully incorporated in the field of view of the diffusion-MRI scan, resulting in partial coverage of the medial lemniscus at the lower border of the scan. To overcome this problem, alternative seed masks for tractography were selected until reasonable coverage was achieved (de Groot et al., 2015). This correction was treated as a potential confounder in all models that included the medial lemniscus (see Section 2.7).

2.4. Assessment of cognitive function

Cognitive function was assessed in all the participants with the following cognitive test battery: 15-Word Learning Test (15-WLT),

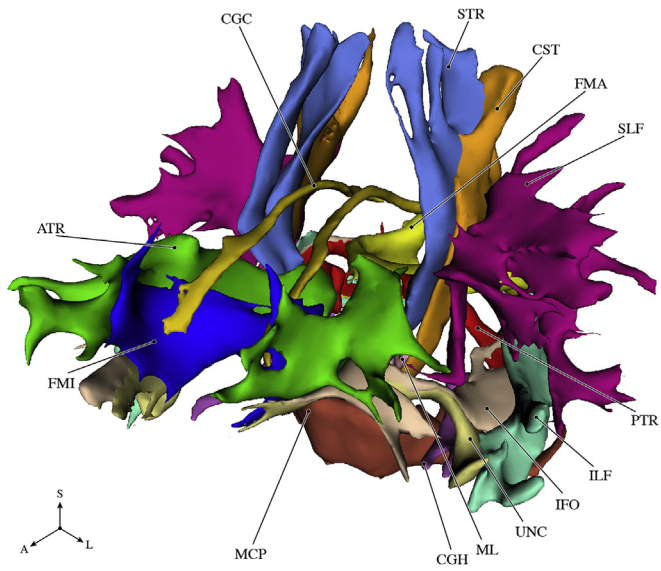

Fig. 1. Overview of white matter tracts. Abbreviations: A, anterior; ATR, anterior thalamic radiation; CGC, cingulate gyrus part of cingulum; CGH, parahippocampal part of cingulum; CST, corticospinal tract; FMA, forceps major; FMI, forceps minor; IFO, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; L, lateral; MCP, middle cerebellar peduncle; ML, medial lemniscus; PTR, posterior thalamic radiation; S, superior; SLF, superior longitudinal fasciculus; STR, superior thalamic radiation; and UNC, uncinated fasciculus.