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学位の種類	博　士　（医　学）
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学位論文題目	Diagnosis of amyloid-positive mild cognitive impairment using structural magnetic resonance imaging: The worth of multiple regions of interest. （構造的核磁気共鳴画像法を用いたアミロイド陽性軽度認知機能障害患者の診断法：複数関心領域の有用性）
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別紙様式３

論 文 内 容 要 旨

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学位論文題目	Diagnosis of amyloid-positive mild cognitive impairment using structural magnetic resonance imaging: The worth of multiple regions of interest. (構造的核磁気共鳴画像法を用いたアミロイド陽性軽度認知機能障害患者の診断法：複数関心領域の有用性)		

Objective: Briefly to compare twin and multiple regions of interest (ROIs) in structural magnetic resonance image (sMRI) diagnosis, testing two statistical parametric mapping (SPM) packages against amyloid status in patients diagnosed with mild cognitive impairment (MCI), who underwent positron emission tomography with Pittsburg compound B (PiB-PET). The packages were Voxel-based Specific Regional Analysis system for Alzheimer's Disease (VSRAD) and Brain Anatomical Analysis using DARTEL (BAAD).

Subject data: Data on 65 patients diagnosed with MCI, who had undergone both sMRI scans and PiB-PET beta-amyloid imaging, were downloaded from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. Of those 65 MCI cases, 18 were found positive by PiB-PET.

Data Processing: BAAD interprets sMRI both in false-color images and in Z-scores for 98 brain regions. VSRAD also gives a false-color picture, and just one bilateral-twin-ROI z-score, usually for the region of the hippocampus and entorhinal cortex, with ROI-locations specified in MNI coordinates.

Results and Discussion: Receiver operating characteristic (ROC) curves were used to measure the reliability of discrimination with each set of ROIs, by the area under the curve (AUC). Test indices such as AUC and accuracy scores seem much better when discriminating large differences than small ones, so that high AUC and accuracy scores are easier to achieve between AD and normal controls than between the amyloid-positive and -negative MCI cases studied here. Because the sorts of memory impairment which attract a clinical diagnosis of MCI are all likely to involve no more than moderate hippocampus dysfunction, discrimination is much less easy with this MCI sample, and lower AUC scores would be expected when the hippocampal region is studied. VSRAD has been widely used and trusted for AD diagnosis in Japan for some years, and in the present study it scored an AUC of only 0.68, showing that the minimum BAAD result (AUC = 0.69) was in a plausible range.

（備考）１．論文内容要旨は、研究の目的・方法・結果・考察・結論の順に記載し、２千字程度でタイプ等で印字すること。

Using BAAD and comparing the results of various selections of ROIs indicated several principles. First, AUC figures increased as more ROIs were added, up to 0.86 for 12 or more (bilateral) ROIs. Second, some ROIs contribute significantly more than others; for example, the parahippocampal gyrus contributes approximately as much as the posterior cingulum + fusiform gyrus + inferior temporal regions. Third, not all the ROIs which appeared significant were contiguous. Fourth, regions also varied in significance asymmetrically between the left and right sides of the brain. As a result, by *post-hoc* "cherry-picking" selective sets of (mostly unilateral) regions, AUC could be increased to almost 0.98 with 11 empirically selected ROIs. However, this study used a relatively small sample, and all these results will need validation when further MRI+PET data become available.

Atlas components, as incorporated in BAAD, define standard brain regions and are crucial for the exchange and comparison of z-scores and other data, especially for multicenter studies, perhaps in combination with other acquisition protocols (e.g., MRS and DTI) and with other software packages. They are also necessary for multi-ROI studies.

Multi-ROI studies are necessary for fuller use of MRI data, and are more valuable than the type of protocol established in VSRAD. First, the hippocampus/entorhinal region is an insufficient biomarker. Those regions may be neither the earliest nor the only regions where AD really appears, and a number of studies have identified atypical varieties of AD, some of which spare the hippocampus. Second, the hippocampus/entorhinal region is an unreliable, non-specific biomarker. Atrophy similar or identical to that caused by AD is also caused by other diseases including AGD, FTD, HCScl, SD, and VaD. Third, no neurodegenerative disease is known to protect against others, so multiple pathologies are not only possible but reportedly common.

Accordingly, atlas-based multi-ROI studies not only facilitate multi-center studies, but should also allow more sensitive, earlier, and comprehensive discrimination not just of AD pathology but of other pathologies too.

Conclusions: Our results indicated that the multi-ROI approach offers greater versatility and better discrimination of the amyloid-positive MCI cases, improving the prospect of data-acquisition and diagnosis earlier than the MCI stage. Both the number and selection of ROIs are crucial to accuracy. Further testing will be needed to validate ROI combinations for MCI and earlier stages, for other populations and pathologies, and for mixed pathologies.

別紙様式８（課程・論文博士共用）

学位論文審査の結果の要旨

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（学位論文審査の結果の要旨）（明朝体１１ポイント、６００字以内で作成のこと。）

認知症の多くはアルツハイマー病によるが、症状の出る前にアルツハイマー病と診断することは治療にとって重要である。PET が診断に使用されるが、MRI の方が侵襲が少なく、汎用性が高い。しかし、現時点では早期診断には PET の方が MRI より正確である。早期診断に MRI を使用するために、使用可能な 65 検体の MRI データを解析し、より正確な診断法の開発を行った。その結果、

1）解析ソフト BAAD は 98 領域を測定できるので、VSRAD の限定された両側 2 領域(hippocampus)の解析より多くの部位を解析できる。その結果、より多くの領域を解析した方が正確性が増すことが明らかになった。
2）特異度と感度が最も高かったのは、左扁桃体など 10 領域を選んで解析した場合で、従来重要と考えられていた hippocampus は含まれていなかった。

以上の結果から、BAAD の多領域解析は、アルツハイマー病と他の疾患の混在した病態の診断や、より早期のアルツハイマー病との診断にも応用できる可能性があることが明らかとなった。

本論文は、BAAD の多領域解析は、アルツハイマー病の早期診断に有用であることを示したものであり、最終試験として論文内容に関連した試問を受け合格したので、博士（医学）の学位論文に値するものと認められた。

（総字数　547 字）

（平成２７年８月３１日）