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# Heritability of Hippocampal Formation Sub-region Volumes

**Kiefer S Greenspan[1,2], Claire R Arakelian[1] and Theo GM Van Erp[1]**

[1]Department of Psychiatry and Human Behavior, School of Medicine, University of California, Irvine, CA 92617, USA

[2]Department of Psychiatry, University of Pittsburgh School of Medicine, Pennsylvania, PA 15261, USA

**Corresponding author:** Theo GM Van Erp, Department of Psychiatry and Human Behavior, School of Medicine, University of California, Irvine, 5251 California Avenue, Suite 240, Irvine, CA 92617, USA, Tel: (949) 824-3331, Fax: (949) 924-3324; E-mail: tvanerp@uci.edu

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## Abstract

**Background:** Hippocampal formation (HF) volume and episodic memory performance are substantially heritable, but HF sub-region heritability estimates and their possible shared genetic variance with episodic memory performance remain to be determined.

**Methods and findings:** This study provides heritability estimates for hippocampal sub-regions (e.g. Cornu Amonis, Subiculum, Parasubiculum, Molecular and Granule Cell Layers of the Dentate Gryus) and Total HF volumes obtained using FreeSurfer 6.0. In addition, this study assesses the heritability of object sequence and verbal episodic memory performance, and the amount of shared genetic variance between HF sub-regions and Total HF volume and episodic memory performance. HF volumes were obtained from high-resolution brain scans from a sample of 499 siblings (mean age ± SD=30.0 ± 3.1, 203 men), including 51 monozygotic and 46 dizygotic twin pairs and 305 non-twin siblings, collected by the Human Connectome Project (www.humanconnectome.org). Heritability estimates for HF sub-regions ranged from 0.42-0.87 and shared genetic variance of HF sub-regions with hippocampal volume was substantial (mean=0.79, range=0.50-0.98). HF sub-region volumes residualized for Total HF and percent HF sub-region volumes were also found to be substantially heritable (range=0.04-0.86 and 0.07-0.84, respectively). Verbal ($h^2$=0.47) but not object sequence episodic memory was found to be significantly heritable; though the amount of shared genetic variance between HF sub-regions and verbal episodic memory was low (mean=0.10, range=0.01-0.20).

**Conclusion:** These findings suggest that HF sub-region volumes are heritable and can be used as quantitative phenotypes in genetic association studies. The low shared genetic variance between HF sub-regions and verbal episodic memory suggests that quantitative trait analyses may not benefit from including both HF volume and episodic memory as bivariate traits in healthy individuals. The extent to which HF sub-region volumes share genetic variance with neuropsychiatric disorders, and as such add value to our ability to identify genetic risk loci for these disorders, remains to be determined.

**Keywords:** Hippocampal formation; Sub-region; Subfield; Heritability; Human Connectome Project; Twin

## Introduction

Overall hippocampal formation volume, either measured by manual tracing or by automated methods, is significantly heritable with estimates in the range of 0.40 to 0.80 [1,2]. Episodic memory, a cognitive function known to depend on the hippocampal formation, is also significantly heritable with estimates in the range of 0.30 to 0.60 [3]. However, heritability estimates of hippocampal formation sub-regions and possible shared genetic variance between sub-regions and episodic memory measures have not yet been reported on. Genome wide association studies (GWAS) have already identified loci significantly associated with hippocampal volume [4,5] and episodic memory performance [6]. The determination of heritability of hippocampal formation sub-region volumes is important because sub-regions may provide additional quantitative traits [7,8] that can be used in genetic association analysis studies, in particular in the search for genes that convey vulnerability to neuropsychiatric disorders. Moreover, evidence of significant shared genetic variance between hippocampal formation and episodic memory measures could allow for bivariate quantitative trait loci (QTL) association and linkage analyses, which can be more powerful than univariate QTL analyses [9].

The hippocampal formation is comprised of Cornu Amonis regions 1-4 (CA1-CA4), the dentate gyrus, and the subiculum. A recent review has hypothesized differential subfield involvement in several neuropsychiatric disorders [10]. Overall hippocampal and hippocampal sub-region volume abnormalities have been reported in many neuropsychiatric disorders, including schizophrenia [11-13], bipolar disorder [13,14], depression [15], post-traumatic stress disorder [16], Alzheimer's disease [17], and mild cognitive impairment [18].

This study estimates the heritability of hippocampus subfield volumes based on the Human Connectome Project's [HCP] extended twin sample [19]. The study assessed hippocampal subfield volumes using Freesurfer 6.0 [20,21], which provides volumes for Cornu Amonis regions 1, 2 and 3 combined, and 4 (CA1, CA2/3, and CA4), Fimbria, Hippocampal

Fissure, Presubiculum, Subiculum, Hippocampal Tail, Parasubiculum, GCMLDG [Molecular (ML) and Granule Cell Layers (GC) of the Dentate Gryus (DG)], Molecular Layer, and the Hippocampal Amygdala Transition Area (HATA). In addition, this study estimates the heritability of HF sub-regions controlling for Total HF volume and the shared additive genetic variance between sub-regions and Total HF volume and episodic memory performance. To control for Total HF volume we performed heritability analyses of sub-region volumes residualized for total HF volume as well as analyses of percent (of Total HF) sub-region volumes. We hypothesized that 1) HF sub-region volumes are significantly heritable, and 2) that they share genetic variance with Total HF volume and episodic memory measures.

# Materials and Methods

## Participants

Prior to study commencement, the use of de-identified Human Connectome Project (HCP) data was determined non-human subjects research by the University of California, Irvine Institutional Review Board. In addition, all authors obtained permission from the HCP to work with both the unrestricted and restricted HCP data. Five-hundred-and-eleven bias-field corrected, high-resolution, twin and sibling, T1-weighted brain scans (T1w/T1w_acpc_dc_restore.nii) were downloaded from the HCP database (www.humanconnectome.org). We excluded: a) one scan that showed poor HF segmentation based on visual inspection, b) 8 singletons, which are not informative in heritability analyses, and c) 3 subjects who were missing episodic memory performance [NIH Toolbox Picture Sequence Memory Test (PSMT) or Penn Word Memory Test (PWMT)] data. The final study sample comprised 51 monozygotic (MZ) and 46 dizygotic (DZ) twin pairs and 305 non-twin siblings (n=499; **Table 1**).

**Table 1** Sample demographics.

| **Human Connectome Project Sample (n=499)** | | |
|---|---|---|
| Age at Scan in Years (SD) | | 29.2 (3.5) |
| Sex (Men/ Women) | | 203/296 |
| Ethnicity (Not Hispanic/ Hispanic/ Unknown) | | 446/52/1 |
| MZ Twin Pairs/ DZ Twin Pairs/ Siblings | | 51/46/305 |
| Race | White | 364 |
| | Black or African American | 111 |
| Asian/ Native Hawaiian | | 9 |
| Mixed | | 5 |
| Unknown | | 10 |
| Education in Years (SD)[a] | | 14.8 (1.9) |
| Handedness (Right/ Left/ Ambidextrous) | | 428/38/33 |
| [a] Estimated from 489 subjects. | | |

## Image acquisition parameters

The HCP high-resolution, sagittal, T1-weighted (MP-RAGE) scans (TR/TE/TI=2400/2.14/1000 ms, flip angle=8°, FOV=224 $mm^2$, in-plane resolution=320 × 320, 256 slices, 0.7 $mm^3$ isotropic voxels, GRAPPA Acceleration factor=2) were acquired with a 3 Tesla Siemens Skyra scanner equipped with a 32-channel head coil at the University of Minnesota (for details see HCP_S500_Release_Appendix_I.pdf on the HCP website).

## Image processing

Left and right hippocampal formation (HF) sub-region, total HF, and total intracranial volumes were extracted using FreeSurfer 6.0 [20,21], which is currently available to the public as part of the FreeSurfer development release (ftp://surfer.nmr.mgh.harvard.edu/pub/dist/freesurfer/dev).

FreeSurfer 6.0 HF sub-regions [21] are based on an ultra-high resolution (0.13 $mm^3$ isotropic voxels) *ex-vivo* atlas and include Cornu Amonis regions 1, 2 and 3 combined, and 4 (CA1, CA2/3, and CA4), Fimbria, Hippocampal Fissure, Presubiculum, Subiculum, Hippocampal Tail, Parasubiculum, GCMLDG [Molecular (ML) and Granule Cell Layers (GC) of the Dentate Gryus (DG)], Molecular Layer, HATA (Hippocampal Amygdala Transition Area), and Total HF (**Figure 1**). Given no known differences in left and right HF laterality, for each subject mean of left and right HF sub-region volumes were computed for heritability analyses (**Table 2**, Volume). In addition to HF sub-region volumes, we also computed the percent sub-region volume of the Total HF [(HF sub-region volume/Total HF

volume) * 100%], a phenotype that should be largely independent from overall HF volume (**Table 2,** Percent).

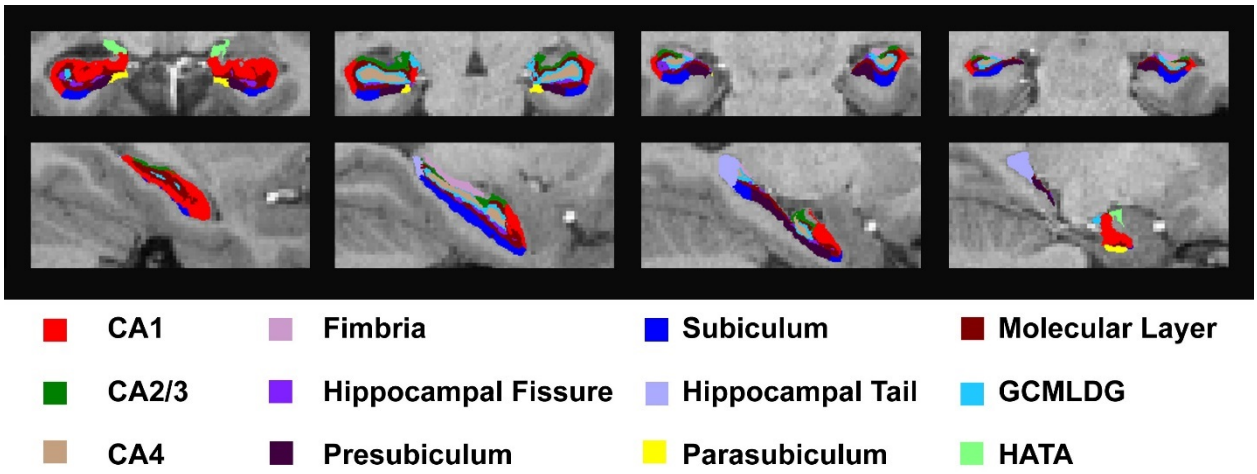


**Figure 1** FreeSurfer 6.0 hippocampal sub-region segmentations.

**Table 2** Absolute means.

| Parameters | Volume | Percent |
|---|---|---|
| **Hippocampal Formation Measures** | | |
| CA1 | 659 (72) | 18.6 (0.8) |
| CA2/3 | 211 (26) | 6.0 (0.5) |
| CA4 | 261 (26) | 7.4 (0.3) |
| Fimbria | 94 (16) | 2.7 (0.4) |
| Hippocampal Fissure | 137 (19) | 3.9 (0.5) |
| Presubiculum | 322 (36) | 9.1 (0.6) |
| Subiculum | 441 (47) | 12.5 (0.6) |
| Hippocampal Tail | 521 (66) | 14.7 (1.4) |
| Parasubiculum | 68 (10) | 1.9 (0.2) |
| Molecular Layer | 587 (56) | 16.6 (0.3) |
| GCMLDG | 305 (30) | 8.6 (0.3) |
| HATA | 65 (8) | 1.8 (0.2) |
| Total HF | 3534 (331) | -- |
| **Episodic Memory Measures** | | |
| PSMT | 111.1 (13.5) | --- |
| PWMT | 35.4 (3.0) | -- |

Mean absolute volumes are in $mm^3$ (SD). Percent=(HF sub-region/ Total HF) *100%. PSMT=NIH Toolbox Picture Sequence Memory. PWMT=Penn Word Memory Test. The mean Intracranial Volume (SD) for the sample was 1556 (185) $cm^3$.

## Quality assurance

Quality assurance (QA) procedures included 1) visual inspection of sagittal snapshots of HF sub-region segmentations overlaid on corresponding T1-weighted anatomical images, created using Freesurfer's Freeview called by custom in-house scripts, and 2) inspection of normal distributions of all HF sub-region volumes. No significant motion artifacts were detected on any of the scans. One twin subject's HF data was eliminated based on poor quality of the HF segmentation.

## Episodic memory measures

The Human Connectome Project assessed object episodic memory with the NIH ToolBox Picture Sequence Memory Test (PSMT) and verbal episodic memory with the Penn Word Memory Test (PWMT). In the PSMT subjects have to recall the order of series of 6 to 18 images. The number of images presented depends on the age of the subjects. Points are given for each correctly recalled adjacent set of images. The total test score is the sum of the points converted to a theta score based on item response theory (IRT; see http://www.nihtoolbox.org/HowDoI/Pages/ScoringAndInterpretation.aspx). The PWMT provides subjects with a list of 20 words to remember. Subjects are then given a second list of 40 words, comprised of 20 targets and 20 foils, and are asked whether each word was on the first list. Options are "definitely yes," "probably yes," "probably no," and "definitely no." The total accuracy score is the number of correctly identified targets (with "definitely yes," "probably yes," responses) and foils (with "probably no," and "definitely no" responses). Given that age is covariate in the heritability analyses, the unadjusted (for age) scores for each of the tests were used in the heritability analyses.

## Statistical analysis

Prior to the heritability analyses, HF sub-region, hippocampal, and ICV volumes were examined for normality via visual inspection of normal distribution plots (Proc Univariate, SAS v9.2, SAS Institute Inc.). Univariate and bivariate heritability analyses were performed using SOLAR version 6.6.2 [22,23], which fits a mixed model that estimates additive polygenetic (g), household or common environment (c), and unique environment or error variance (e). The significance of heritability is determined by comparing the housepoly (ACE) with the poly (AE), and sporadic (g=0) models and the poly (AE) model with a sporadic (g=0) model based a chi-square tests with df=1 (the difference in the number of terms in the model). The univariate models computed heritability estimates for the HF sub-region, Total HF, and ICV volumes as well as PSMT and PWMT episodic memory performance measures. The bivariate models estimated the amount of shared genetic variance (RhoG) between the HF sub-regions and Total HF (FS 6.0 Whole hippocampus label) volume and HF sub-regions and episodic memory performance. All models included sex and age as covariates (Model 1). The univariate heritability analyses were also run including Total HF volume as an additional covariate (Model 2, HF sub-regions residualized for Total HF volume), and with the percent HF sub-region (of total HF volume) as traits, which may provide useful quantitative phenotypes that are independent from Total HF volume. False discovery rate (FDR) was used to control for multiple comparison correction [24].

# Results

## Heritability estimates

The heritability estimate for Total HF volume was 0.87. Univariate heritability estimates for HF sub-regions ranged from 0.20 to 0.83 and were significant (FDR corrected) for all regions with exception of the fimbria (**Table 3**, Model 1). Additionally, heritability estimates of HF subfield volumes residualized for Total HF volume (**Table 3**, Model 2) ranged from 0.04 to 0.86 and the heritability estimates for percent HF subfield volumes ranged from 0.07 to 0.84 (**Table 3**, Percent), and were significant (FDR corrected) for all regions except for the fimbria, hippocampal fissure, and HATA. Verbal episodic memory, as measured with the PWMT was significantly heritable ($h^2$=0.47), while object sequence episodic memory as measured with the NIH Toolbox PSMT was not ($h^2$=0.29; **Table 3**).

**Table 3** Heritability of hippocampal formation and episodic memory measures.

| | Model 1 | | | | Model 2 | | | | Percent | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $h^2$ | p-value | $c^2$ | p-value | $h^2$ | p-value | $c^2$ | p-value | $h^2$ | p-value | $c^2$ | p-value |
| **Hippocampal Formation** | | | | | | | | | | | | |
| CA1 | 0.83 | 1.07E-18 | | | 0.70 | 4.69E-15 | | | 0.69 | 6.19E-15 | | |
| CA2/3 | 0.81 | 1.52E-13 | | | 0.86 | 1.27E-18 | | | 0.84 | 5.46E-18 | | |
| CA4 | 0.79 | 1.09E-14 | | | 0.65 | 4.19E-10 | | | 0.63 | 4.98E-10 | | |
| Fimbria | 0.20 | 2.12E-01 | 0.30 | 1.26E-02 | 0.04 | 4.47E-01 | 0.30 | 3.17E-02 | 0.07 | 4.00E-01 | 0.26 | 4.92E-02 |
| Hip. Fissure | 0.53 | 9.43E-09 | | | 0.47 | 1.88E-02 | 0.08 | 2.89E-01 | 0.43 | 1.84E-02 | 0.14 | 1.40E-01 |
| Presubiculum | 0.64 | 1.06E-04 | 0.13 | 1.20E-01 | 0.66 | 3.18E-13 | | | 0.62 | 1.34E-11 | | |
| Subiculum | 0.83 | 1.81E-23 | | | 0.69 | 3.96E-17 | | | 0.69 | 5.17E-17 | | |
| Hip. Tail | 0.82 | 1.89E-20 | | | 0.75 | 6.64E-19 | | | 0.73 | 2.39E-05 | 0.02 | 4.21E-01 |
| Parasubiculum | 0.65 | 2.18E-04 | 0.06 | 3.05E-01 | 0.56 | 1.82E-08 | | | 0.49 | 6.00E-07 | | |
| Molecular Layer | 0.81 | 6.00E-19 | | | 0.63 | 5.57E-14 | | | 0.63 | 3.00E-14 | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| GCMLDG | 0.81 | 2.21E-16 | | | 0.67 | 2.14E-10 | | | 0.65 | 5.72E-10 | | |
| HATA | 0.62 | 1.69E-04 | 0.12 | 1.39E-01 | 0.45 | 2.20E-02 | 0.13 | 1.59E-01 | 0.38 | 5.29E-02 | 0.15 | 1.29E-01 |
| Total HF | 0.87 | 1.71E-23 | | | | | | | | | | |
| **Episodic Memory** | | | | | | | | | | | | |
| PSMT | 0.29 | 1.00E-01 | | | | | | | | | | |
| PWMT | 0.47 | 1.00E-07 | | | | | | | | | | |

$h^2$=Heritability estimate, $c^2$=Common environment variance component estimate. HF sub-region heritability estimates that survive the false discovery rate (FDR) multiple comparison correction is underlined. For comparison purposes, the heritability estimate for intracranial volume is 0.88 (p=1.21E-31).

## Shared genetic variance

Bivariate heritability analyses showed that the mean shared genetic variance (RhoG) between HF sub-regions and Total HF volume was 0.79 (range=0.50 - 0.98). Phenotypic correlations (RhoP) between HF sub-region volumes and the hippocampus volumes ranged from 0.46 to 0.97 (**Table 4**, Total HF). The mean shared genetic variance (RhoG) between HF sub-regions and verbal episodic memory performance as measured by the PWMT was small (mean=0.10, range=0.01-0.20) as were the phenotypic correlations (**Table 4,** PWMT).

**Table 4** Shared genotypic and phenotypic variance of hippocampal formation sub-regions with hippocampal volume and PWMT.

| | **Total HF** | | **PWMT** | |
|---|---|---|---|---|
| | **RhoG (SE)** | **RhoP** | **RhoG (SE)** | **RhoP** |
| CA1 | 0.91 (0.01) | 0.90 | 0.14 (0.11) | 0.08 |
| CA2/3 | 0.69 (0.04) | 0.70 | 0.04 (0.12) | 0.03 |
| CA4 | 0.91 (0.02) | 0.89 | 0.09 (0.12) | 0.07 |
| Fimbria | 0.67 (0.06) | 0.50 | 0.04 (0.12) | 0.07 |
| Hippocampal Fissure | 0.50 (0.07) | 0.46 | 0.20 (0.14) | -0.01 |
| Presubiculum | 0.78 (0.04) | 0.73 | 0.07 (0.10) | 0.08 |
| Subiculum | 0.90 (0.02) | 0.88 | 0.10 (0.10) | 0.10 |
| Hippocampal Tail | 0.69 (0.04) | 0.65 | 0.20 (0.11) | 0.07 |
| Parasubiculum | 0.72 (0.09) | 0.52 | 0.01 (0.11) | 0.10 |
| Molecular Layer | 0.98 (0.003) | 0.97 | 0.11 (0.11) | 0.09 |
| GCMLDG | 0.93 (0.01) | 0.92 | 0.06 (0.11) | 0.06 |
| HATA | 0.76 (0.04) | 0.68 | 0.08 (0.10) | 0.14 |
| Total HF | | | 0.12 (0.10) | 0.09 |

RhoG=Shared genotypic variance, RhoP=Shared phentotypic variance, HF=Hippocampal Formation.

# Discussion

The main findings of this study are 1) HF sub-region volumes obtained using FreeSurfer 6.0 and verbal memory performance as measured by the Penn Word Memory Test are significantly heritable, and 2) HF sub-regions volumes, in predominantly healthy individuals, share a significant amount of genetic variance with overall hippocampal volumes but only a limited amount of genetic variance with verbal episodic memory as measured by the Penn Word Memory Test.

The heritability estimates for HF sub-regions observed in this study, based on Human Connectome Project (HPC), closely resemble those recently reported based on the Queensland Twins Imaging Study (QTIM): heritability for all regions, except the fimbria differed by less than 0.10 [25]. One interpretation of our findings is that almost all hippocampal subfields are substantially heritable. Only the heritability estimate for the fimbria was not significant in this study. It is possible that this is due to lower reliability of smaller brain regions, though the parasubiculum and HATA regions are of similar size and did show significant heritability.

An alternative interpretation, predominantly based on the finding of a large amount of shared genetic variance between the hippocampal sub-region and whole hippocampal volumes, is that the 0.7 $mm^3$ isotropic voxels do not provide sufficient resolution to discriminate at least some individual HF sub-

regions. When the resolution of the scans is insufficient, the volumes of the HF sub-regions may predominantly be determined by Total HF volume, and the HF sub-region heritability estimates may simply reflect Total HF volume heritability. While, we cannot fully distinguish between these two alternative interpretations, the fact that 9 out of 12 HF sub-region volumes residualized for Total HF volumes were significantly heritable, and b) the same 9 out of 12 percent HF volumes were also significantly heritable suggests that the FreeSurfer 6.0 method is able to reliably measure variation in HF sub-regions at the 0.7 $mm^3$ isotropic voxel resolution. Family studies using data with higher resolution scans will be needed to firmly address these distinct possibilities.

Strengths of the study include 1) the extraction of hippocampal sub-region volumes from a publically available extended twin sample with high quality, high-resolution (0.7 $mm^3$ isotropic) structural imaging data collected by the Human Connectome Project [19]; 2) the use of publically available FreeSurfer version 6.0, which allows for the estimation of HF sub-region volumes based on a high-resolution post-mortem template that addresses a number of issues raised about prior versions of the software [26]; 3) the visual inspection of hippocampal segmentations performed on the segmentations for each individual subject; 4) the use of the ACE (SOLAR's housepoly) model for heritability estimation, a model that includes the common environment term to help avoid overestimation of heritability effects; 5) the use of FDR multiple comparison correction, and 6) the estimation of HF sub-region heritability controlling for Total HF volume (both sub-regions residualized for Total HF as well as percent HF sub-region).

A shortcoming must also be noted. While the HF sub-region heritability analyses were arguably performed on the highest resolution extended twin structural imaging data set, it is not fully clear whether the 0.7 $mm^3$ isotropic voxel size of images provides sufficient resolution to adequately dissociate HF sub-regions.

There are numerous manual [27] and automated [21,28-31] methods to assess hippocampal sub-regions. The opportunities provided by these tools drive the need for the collection of new high-quality, high-resolution brain scans to improve our understanding of the role of hippocampal circuitry in health and disease.

In conclusion, hippocampal formation sub-region volumes are heritable and therefore can be used as quantitative traits in genetic association and linkage studies. In healthy individuals, HF sub-regions share substantial additive genetic variance with overall hippocampal volumes (between 50% to 98%). The field of high-resolution hippocampal imaging needs more data to provide guidance on the minimum resolution required to properly dissociate HF sub-regions. Finally, the extent to which individual HF sub-regions differ in terms of their shared genetic variance with neuropsychiatric disorders and the extent to which they add value to our ability to identify genetic risk loci for these disorders remain to be determined.

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## Conflict of Interest

Dr. Van Erp has consulted for Roche Pharmaceuticals and has contract with Otsuka Pharmaceutical Co. Ltd. (OPCJ). The remaining authors declare no potential conflict of interest.

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