Current Opinion in Behavioral Sciences on "Deep Imaging - Personalized Neuroscience"

Deep characterization of individual brain-phenotype relations using a multilevel atlas

Christiane Jockwitz[1,2], Nora Bittner[1,2], Svenja Caspers[1,2*], Katrin Amunts[1,3*]

[1]*Institute of Neuroscience and Medicine (INM-1), Research Centre Jülich, Jülich, Germany*
[2]*Institute for Anatomy I, Medical Faculty, Heinrich Heine University and University Hospital Düsseldorf, Düsseldorf, Germany*[3]*C. and O. Vogt Institute for Brain Research, Heinrich Heine University Düsseldorf and University Hospital Düsseldorf, Germany*

*These authors contributed equally

Highlights describing concisely the main results of your paper (max. 85 characters including spaces):

- Multimodal profiling deciphers inter-subject variability at individual level
- Heterogeneous individual cognitive, lifestyle, and atrophy profiles
- Deep characterization of five older males being at risk for dementia as a use case
- Multilevel atlas information revealed (dis-)similarities of atrophied brain regions
- Personalized neuroscience requires integration of multifactorial/multilevel data

Abstract (max 120 words)

Population neuroimaging allows for extracting general principles of brain-phenotype relationships. Capturing individual brain-behavior profiles in groups with pronounced inter-individual variability, like the older adult population, however, remains challenging. Therefore, deep characterization is required to link multilevel brain, cognitive and lifestyle data. We here proposed a use case of five older males scoring low on a dementia screening test. We showed quite heterogeneous individual cognitive, lifestyle and grey matter atrophy profiles. Integrating additional regional genetic, molecular and connectional data using a multilevel atlas framework revealed (dis-) similarities between the atrophied brain areas, thereby helping to explain the individual phenomena and emphasizing the need for integrating multifactorial and multilevel information on the way toward individualized predictions.

Introduction

One of the major goals in modern population neuroimaging is the extraction of robust trends of brain-phenotype relationships to understand general principles of human brain organization under healthy conditions, and capture transitions to disease. The challenge of extracting such trends, however, lies in the high inter-individual variability including variations at the level of behavior, brain structure and function, and age-dependent changes [1, 2]. During the last decade multicenter studies and imaging consortia, such as ENIGMA (Enhancing Neuro Imaging Genetics through Meta-Analysis [3]), UK Biobank [4], Human Connectome Project [5], Rotterdam study [6], ADNI (Alzheimer Disease Neuroimaging Initiative[7]) and NAKO (German National Cohort [8]) have been established that capitalize on large sample sizes to increase statistical power which in turn allows for a more robust identification of various sources for inter-individual variability along the different levels.

The older adult population represents a prime example for a particularly high inter-individual variability. Studies have indicated signs of cognitive decline [9, 10] and brain atrophy [11] from early to late adulthood, but also adaptions of the brain's functional network architecture [12, 13]. Focusing on older age, though, reveals high inter-individual differences in these features going beyond what can be explained by the factor 'age' alone [1, 14, 15]. Rather, changes in brain structure and/or functional connectivity have been associated with inter-individual differences in cognitive performance [16], lifestyle [17, 18], sex [3], genetic predispositions [19], and/or environmental influences [20]. It has to be mentioned, though, that the influence of such factors is typically rather small. Smoking habits, e.g., only explain 4 % of the variability of cortical thinning in older adults [21]. Furthermore, effects of different influencing factors might interact and lead to (non-) additive effects. Along a similar line of reasoning, the risk for developing neurodegenerative diseases, i.e. Alzheimer's disease (AD), increases with age. Nevertheless, at the age of 70, 10% of the population develop AD, while the remaining 90% do not [22]. Previous studies additionally showed that prodromal stages of AD, i.e. subjective or mild cognitive impairments do not necessarily convert into AD over time [23, 24], indicating that other factors than 'age' contribute to the risk for developing such a neurodegenerative disease. Thus, to finally understand normal and pathological aging there is an urgent need to decode the factors that drive this older adult population's variability.

While population-based studies are essential and important, e.g. to build hypotheses and inform brain modeling approaches, analyses on the group level lack an important aspect: Inter-individual variability is often regarded as some kind of unexplainable noise, that cannot be explained by focusing on main effects. Instead, we emphasize to approach variability as a target

of research, to study the different factors contributing to variability in more detail, and to quantify factors characterizing brain-behavior relationships [25].

This requires deep, multifaceted analyses to consider various influencing factors on the individual aging process. Potentially important aspects that explain why some subjects age at a faster rate as compared to others hence require large, phenotypically deep and rich datasets – both in terms of group size, and on the individual level. This allows to derive "individual fingerprints" of phenotypical characteristics and neuronal correlates. Secondly, towards a holistic understanding of brain aging it is necessary to link multilevel brain data, from the molecular and cellular to the systems network level. As many molecular and cellular data are accessible only from post-mortem tissue and not directly available for subjects of large cohorts with systems level neuroimaging and phenotypic data, linkage through a common reference framework can help to fill this gap. We here propose a use case of how to integrate individual deep phenotypic characterization and multilevel brain imaging using data of five older males of a large population-based cohort study, 1000BRAINS [26], as an example. The here selected subjects represent a group of interest. They were defined a priori, based on a standardized dementia screening test in contrast to a large group of age- and sex-matched controls.

Inter-individual variability, deep phenotyping and multilevel brain data: A use case

A use case will illustrate the relevance of individual deep phenotypic characterization, based on cognitive, lifestyle and grey matter atrophy profiles to obtain a deeper understanding of normal and pathological aging, and to develop indicators in the future to distinguish both from each other. We a priori selected five male participants from 1000BRAINS scoring low on a dementia screening test and created individual profiles of cognitive performance, lifestyle measurements and modulated grey matter volume (P1-5). Subsequently, regional genetic, molecular and connectional data were drawn from a multilevel atlas framework based on the Julich Brain atlas (Amunts et al., 2020) as provided in EBRAINS (https://ebrains.eu/services/atlases/brain-atlases/) to identify atrophied brain regions (for a description, see Box 1).

Participants being at risk for dementia (DemTect Score [27] ≤ 8, see Figure 1a) came from 1000BRAINS, a large population-based cohort study assessing the inter-individual variability during aging [26]. Healthy controls (HC) were males from the same cohort, within the same age-range (n=323, mean age: 67.6 ± 6.4), but performed adequate on the dementia screening

test (>12; mean DemTect score: 15.2 ±1.8). To examine the variability of the "at-risk" participants (P1-5), we created cognitive and lifestyle profiles, i.e. individual fingerprints using 19 cognitive [28, 29] and 10 lifestyle features [17, 30] (Figure 1b/c). Higher cognitive scores indicate higher performance. Regarding lifestyle, higher scores indicate protective behavior for the Dietary Index (DI), social behavior (SOC) and physical activity (SP) and risky behavior for alcohol consumption (ALC), body related factors (BODY) and smoking habits (SMO). In order to better assess the individual values (with regard to interpretation and rating in, e.g., good or bad), we also calculated the mean value and SD (dashed gray line in the figures) within the healthy control group.

Participants P1-5 performed at a "at-risk" level regarding the dementia screening test and clearly scored below HC (Figure 1a). At the same time, the cognitive and lifestyle profiles were highly variable, and no common trends were seen for participants P1-5. Differences, however, were seen at an individual level. P1 and P3 generally performed at a lower cognitive level (P1 especially in the domains of attention and language and P3 in the domains of executive functions and language). In turn, P2 and P5 remained within the normal range in almost all cognitive tasks (P5 even performed at a higher level in the language domain) and P4 showed single cognitive abilities to be impaired, i.e. executive functions and working memory (Figure 1b).

With respect to lifestyle, a similarly heterogenous picture has been found (Figure 1c). P1 and P2 seem to be centered around the mean of the HC, with a slightly lower body mass index (BMI) and a slightly healthier diet. P3 had the highest BMI, while P5 had a high amount of packyears (referring to smoking amount during the lifespan) and P4 followed healthier diet, together with a low BMI and higher physical activity. The development of dementia or mild cognitive impairment is assumed to be related to impairments in at least one cognitive domain (e.g. learning and memory), a high BMI, low physical activity, unhealthier diet or high smoking (for recent reviews, see [31, 32]). The individual profiles, however, show that these general trends only partially reflect the situation at the level of the individual subject. Instead, a rather heterogenous picture emerges with each individual showing a mixture of different protective and potentially aversive lifestyle factors [33]. Hence, it rather seems that each individual has its own cognitive/lifestyle fingerprint hinting at multifactorial genesis of cognitive impairment during older ages.

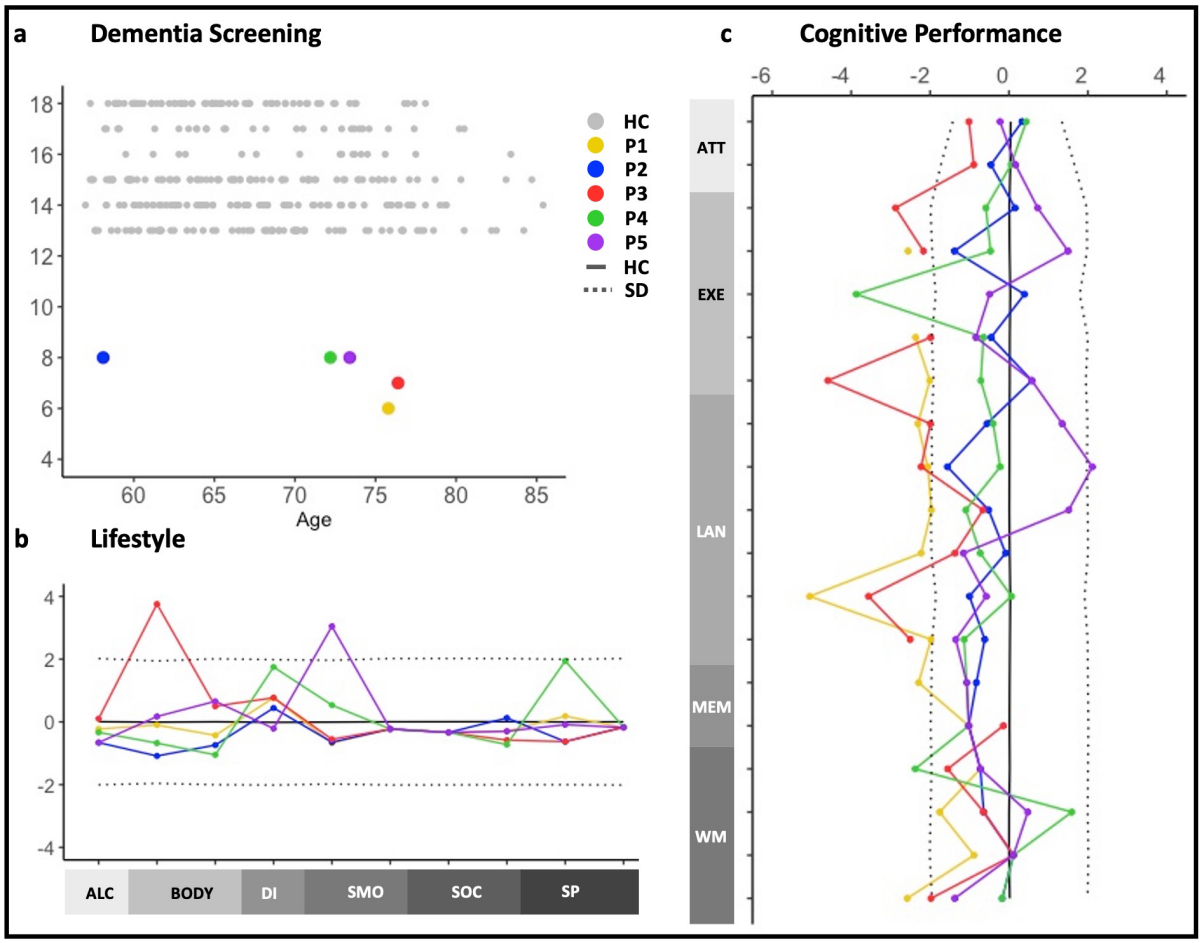


Figure 1: Comparison of participants at risk for dementia (P1-5) with healthy controls (HC) scoring normal in dementia testing where the black line represents the mean of HC and dashed gray lines represent two standard deviations from the mean of HC; a) DemTect score for HC (grey dots) compared to P1-5; b) Lifestyle factors (from left to right: ALC = weekly alcohol consumption; BODY = Body Mass Index, Waist Hip Ratio; DI =Dietary Index; SMO = Packyears, Cigarettes per day; SOC = Family Status, Social Integration Index; SP = Metabolic Equivalent, Walking Stairs); c) Cognitive Performance from top to down: ATT = Attention (Processing Speed, Selective Attention); EXE = Executive Functions (Concept Shifting, Figural Fluency, Interference, Problem Solving); LAN = Language (Naming, phonemic Verbal Fluency, phonemic Verbal Fluency [switching condition], semantic Verbal Fluency, semantic Verbal Fluency [switching condition], Vocabulary; MEM = Memory (Episodic Memory, Figural Memory); WM = Working Memory (verbal short-term Memory, verbal Working Memory, visuospatial short-term Memory, visuospatial Working Memory, visual Working Memory). All cognitive and lifestyle variables, were standardized to facilitate comparability across variables. Discontinued lines between task indicate that one tasks was not performed by the specific subject.

Beyond cognitive alterations and behavioral differences, previous studies reported specific atrophy patterns in healthy subjects during aging as compared to patients suffering from (or being at risk for) dementia [11, 34, 35]. With respect to Alzheimer's disease (AD), the medial temporal lobe would be one of the first regions affected [36], depending on the subtype [35]. In the current participants P1-5, we extracted therefore modulated grey matter volumes values (using the CAT toolbox, SPM12, [37]) for the cytoarchitectonically defined areas of the Julich-Brain atlas [38].

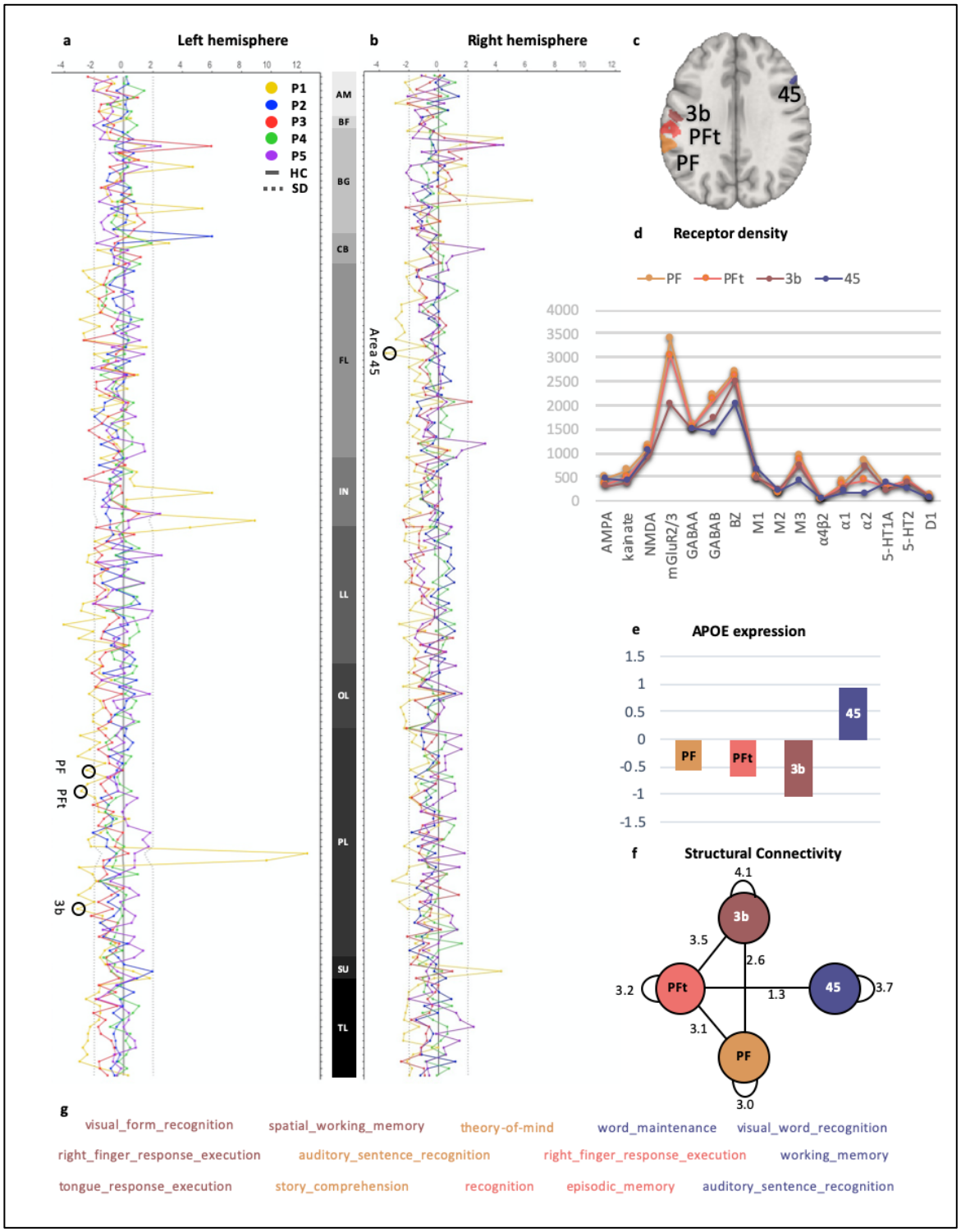


Figure 2: a and b) Grey matter volume [scaled] values of healthy subjects (HC) and participants at risk for dementia (P1-5) for the cytoarchitectonically defined Julich-Brain areas ([38]; www.julich-brain.org) for the left (a) and right (b) hemispheres: AM = Amygdala, BF = Basal Forebrain, BG = Basal Ganglia, CB = Cerebellum, FL = Frontal Lobe, IN = Insula, LL = Limbic Lobe, OL = Occipital Lobe, PL = Parietal Lobe, SU = Subcortical, TL = Temporal Lobe; dashed gray lines represent 2 standard deviations from the mean of the control group; circled data points represent examples of brain regions that deviate more than 2 standard deviations below the mean of the HC (left areas PF, PFt, 3b and area 45 of the right-hemispheric homolog of Broca's region). c) four selected brain regions showing low grey matter volume values in P1 (>2 standard deviations below the mean of the control group) projected on a standard brain (MNI152): areas PF, PFt of the posterior parietal cortex: [39, 40]; 45:[41]; somatosensory area 3b: [42, 43]. d) Receptor fingerprints for the selected brain regions: [44, 45]; e) APOE gene expressions within the four selected brain regions derived from the Allen brain atlas (https://alleninstitute.org/what- we-do/brain-science) analyzed with respect to the Julich Brain areas using JuGEx tool [46]; f) Structural connectivity values (log transformed) between the selected brain regions; g) Individual Brain Charting (IBC) fMRI datasets with exemplary strong activations in the four selected brain regions (left areas PF, PFt, 3b and right 45) derived from [47].

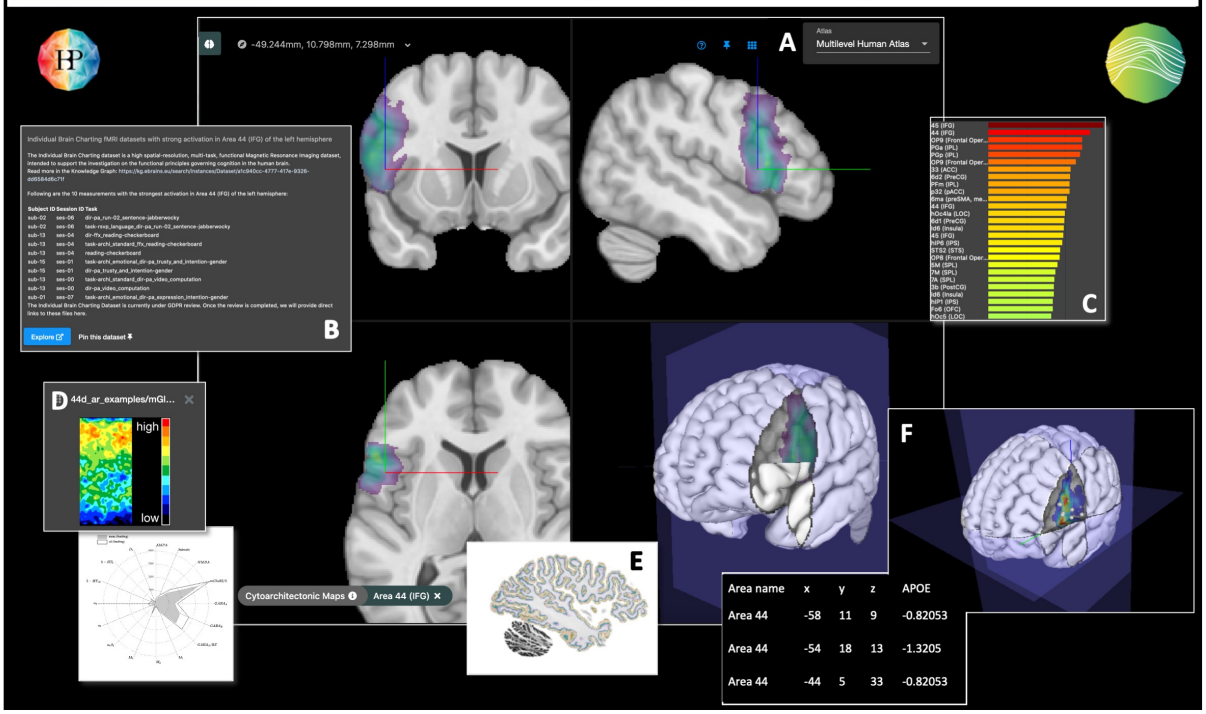
The analysis of the grey matter volume profiles (Figure 2a/b) of P1 showed a variety of deviations from the distribution of HC, across all brain regions. These observations fit to the behavioral profiles, since P1 also showed the most pronounced cognitive impairments. This was different from the lifestyle profile, which was centered around the mean of the HC. In turn, P4 is characterized by high physical activity, a healthy diet together with a lower BMI and social integration in combination with worse performance in some cognitive tasks. In turn, grey matter volume values were centered around the mean of HC. Although cognitively stable across all domains, this was also true for P2, showing lower BMI and a rather healthier diet. P3, with high BMI and selective cognitive impairments, contrarily tended to have gray matter volume values within the lower end of the normal range of HC. P5, who showed a high amount of packyears together with normal to high cognitive abilities, had regionally variable gray matter volume, with some regions showing volume comparable to the upper and some comparable to the lower end of the HC distribution.

The comparison of the participants P1-5 showed, that each of them showed individual rather than common atrophy patterns. These individual profiles do not seem to fit to the atrophy pattern observed in subjects with mild cognitive impairments as shown in a group study (i.e. medial temporal lobe, including the hippocampus [35]; cf. Figure 2a/b). Thus, regardless of the information that has been considered (i.e. cognitive, lifestyle and grey matter atrophy), each of the five "at-risk" subjects seems to have its own brain-phenotype profile. Putting these results into the context of group analyses it needs to be stressed that analyzing the older adult population on an individual level should be an inevitable next step in the neuroscientific community, particularly when it comes to individual treatment or prevention strategies [48].

Deep characterizations of the individual, however, are challenging due to limited availability of individual data, difficulties in integrating heterogenous multilevel information of distinct levels of granularity in one reference space as well as the choice of well suited methodological and statistical approaches. While the current use case described the individual profiles at various levels, i.e. cognition, lifestyle and grey matter volume, to decode the aging brain and its underlying mechanisms, additional information might be needed at molecular, cell and system levels, i.e., ranging from macro to microscopic scales. For example, cellular, molecular and genetic characterizations of the affected brain regions would help to gain insights at the most fundamental level. From a network point of view, the question would be whether the affected brain areas of P1 (e.g. left areas 3b, PF, PFt and right area 45; cf. Figure 2c) would be structurally or functionally connected. Receptor and genetic characterizations of affected brain regions might additionally be of special interest here, since both have been associated with

successful treatment response [49]. Such information can be considered using the EBRAINS multilevel brain atlas, provided by the Human Brain Project (HBP) [50]. This atlas provides a multitude of such data on multiple levels of brain organization in a common reference space with a large number of macro- and microscopic data from different sources (see Box 1).

EBRAINS Research Infrastructure of the HBP provides the interactive atlas viewer (A) that allows for exploring different brain atlases (including the Julich-Brain) integrated on multiple reference spaces. These information are complemented by region-specific information based on a growing set of multimodal datasets including information from neuroimaging studies, e.g. functional imaging (B) or structural connectivity (C), distributions of receptors (D) and cells (E) as well as genetic representation (F) in cytoarchitectonically defined brain regions. For more information, see https://atlases.ebrains.eu/viewer. Besides the interactive viewer, EBRAINS provides programmatic access via Python and HTTP.



Box 1: EBRAINS Interactive Viewer.

We here show exemplarily data provided in EBRAINS for a more in-depth analysis of the individual aging process of participant P1. We assessed four different regions that showed significant brain atrophy (left areas 3b, PF, PFt and right area 45) using EBRAINS to gather multimodal information about these areas.

First, receptor densities of neurotransmitter systems (Figure 2d) show a regionally specific distribution in the brain, are highly relevant for signal transduction in the healthy brain, but also in the pathologically altered brain, and serve as targets for drug therapy [51, 52]. The analysis of receptor data from the atlas indicates that $GABA_B$ receptors seem to be highest in parietal areas PF and PFt, followed by area 3b, and lowest in right area 45 of Broca's region. In turn, the density of the cholinergic receptor M1 for acetylcholine seem to be highest in right 45 compared to left hemispheric brain regions.

Secondly, regional differences in terms of the apoliprotein E (APOE) expression levels, a genetic component that has frequently been associated with AD [53] were found. Specifically,

right area 45 showed a higher APOE expression as compared to the left hemispheric brain regions (Figure 2e).

Third, EBRAINS provides deep information on structural connectivity patterns: Areas 3b, PF and PFt seem to be highly inter-connected whereas right area 45 is only connected to area PFt. Thus, these observations raise the possibility of different networks to be affected in P1, which, in turn, might be related to the general decline in different cognitive domains (Figure 2f).

Fourth, this is further supported by information collected from task-based functional imaging studies investigating a variety of brain functions (Individual Brain Charting (IBC) fMRI datasets [47]). Figure 2g shows exemplary brain-behavior relationships for the selected brain regions: While each brain region seems to be activated during different cognitive tasks, there is also overlap in terms of functions involved, i.e. all four areas seem to be involved in the mental process of recognition. Taken together, the additional multilevel information combining micro- as well as macrostructural information allows for an in-depth characterization of brain-behavior relationships.

Personalized versus Group Analyses

The current use case demonstrated the feasibility of multilevel brain organizational information for enhancing deep characterization of brain-phenotype relations on the individual level. Characterizing the individual subject, in contrast to group averages, might be the inevitable step towards successful diagnostics and treatments, as previously described for, e.g., epilepsy surgery [54-56] or AD [57, 58]. Group analyses follow the principle of “one size fits all” meaning that a group of patients suffering from the same disease or symptom would be treated the same way. Based on the current use case, we urgently need to realize that the here presented individuals show more differences than similarities regarding their individual cognitive, lifestyle and brain atrophy fingerprints. Following, these analyses emphasize the benefit of different treatment strategies on individual subjects, e.g., physical versus cognitive interventions or a combination of both. The impact of personalized medicine is very promising since it allows for individual therapeutic approaches that could be preventive in nature, rather than reactive. It can be expected that individual diagnostics based on factors such as examined in the present study, and /or other factors such as genetics, could finally lead to less side effects after pharmacological treatments [59].Certainly, two aspects must be considered here. First, while it is desirable to characterize an individual with as much data as possible, the question arises as to which aspects are the most important, for example, in order to tailor individual therapies. The analysis of brain-phenotype relationships on the group level, e.g. relying on

statistical comparisons, has different constraints than examining such relations on the individual level, for which tools are needed to estimate the weighted influences and potential relevance of all factors included in an individual fingerprint. Second, since individualized science and personalized medicine focus on individual trajectories e.g., during aging or disease progress, longitudinal data would be highly beneficial to better understand such processes.

Currently, methods and research infrastructure are being built for handling and processing huge amounts of individual data to enable predictions and simulations of effects of factors such as age, sex or disease status on the brain. Machine learning approaches, e.g., have the potential to successfully predict such factors on an individual level based on respective training data [60]. Simulation tools, such as "The Virtual Brain" (https://www.thevirtualbrain.org), build neurobiologically-informed computational models based on potential disease or other relevant mechanisms (e.g. aging), requiring multilevel data (for first applications, see [61, 62]).

Such ongoing efforts require bridging the gap between cellular-molecular and systems level neuroscience. The European Human Brain Project (HBP) aims at integrating information of the brain at multiple scales from different research disciplines via EBRAINS (Box 1), an interactive tool combining multilevel data from various sources to enable enriching subject-specific analyses. The importance of such a platform can be derived from the current use case example: the five "dementia at risk" subjects in the 1000BRAINS study showed individual profiles for various phenotypes, which is accompanied by individual brain atrophy patterns, for which multilevel atlas information revealed commonalities and differences at the connectional, genetic and molecular level potentially explaining parts of the peculiarities.

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References

References of special (*) or outstanding (**) interest:

**Amunts et al., 2019: The authors present and discuss the Human Brain Project (HBP), which explores the multilevel complexity of the brain in space and time, transfers the acquired knowledge to brain-derived applications in health, computing, and technology, and provides shared and open computing tools and data through the HBP European brain research infrastructure.

**Amunts et al., 2020: The authors represent a three dimensional cytoarchitectonic atlas of the human brain that reflects the variability of the brain's structure. The atlas is part of the EBRAINS infrastructure and serves as an interface to link multilevel information on brain structure and function.

*Einevoll et al., 2019: The authors argue and discuss the urgent need for why large-scale model networks of neurons will be indispensable for bridging the scales between neuron and system levels

**Bittner et al., 2019: The authors investigate combined and individual contributions of four lifestyle variables – alcohol consumption, smoking, physical activity, and social integration - to brain structure and functional connectivity in a population-based cohort of 549 older adults.

** Bludau et al., 2018: The authors present an integrated framework, JuGEx, linking gene expression (derived from the Allen Human Brain Atlas; https://alleninstitute.org/what- we-do/brain-science) to cytoarchitectonic brain areas.

*Belloy et al., 2019: This review addresses the importance of APOE in the genesis of Alzheimer's disease.

1. Dickie, D.A., et al., *Variance in brain volume with advancing age: implications for defining the limits of normality.* PLoS One, 2013. **8**(12): p. e84093.
2. Habib, R., L. Nyberg, and L.G. Nilsson, *Cognitive and non-cognitive factors contributing to the longitudinal identification of successful older adults in the betula study.* Neuropsychol Dev Cogn B Aging Neuropsychol Cogn, 2007. **14**(3): p. 257-73.
3. Jahanshad, N. and P.M. Thompson, *Multimodal neuroimaging of male and female brain structure in health and disease across the life span.* J Neurosci Res, 2017. **95**(1-2): p. 371-379.
4. Miller, K.L., et al., *Multimodal population brain imaging in the UK Biobank prospective epidemiological study.* Nat Neurosci, 2016. **19**(11): p. 1523-1536.
5. van Essen, D.C., et al., *The Human Connectome Project: a data acquisition perspective.* NeuroImage, 2012. **62**(4): p. 2222–2231.
6. Hofman, A., et al., *The Rotterdam Study: objectives and design update.* Eur J Epidemiol, 2007. **22**(11): p. 819-29.
7. Jack, C.R., Jr., et al., *The Alzheimer's Disease Neuroimaging Initiative (ADNI): MRI methods.* J Magn Reson Imaging, 2008. **27**(4): p. 685-91.
8. Bamberg, F., et al., *Whole-Body MR Imaging in the German National Cohort: Rationale, Design, and Technical Background.* Radiology, 2015. **277**(1): p. 206-20.

9. Hedden, T. and J.D. Gabrieli, *Insights into the ageing mind: a view from cognitive neuroscience.* Nat Rev Neurosci, 2004. **5**(2): p. 87-96.
10. Schaie, K.W., *"When does age-related cognitive decline begin?" Salthouse again reifies the "cross-sectional fallacy".* Neurobiol Aging, 2009. **30**(4): p. 528-9; discussion 530-33.
11. Walhovd, K.B., et al., *Consistent neuroanatomical age-related volume differences across multiple samples.* Neurobiol Aging, 2011. **32**(5): p. 916-32.
12. Reuter-Lorenz, P.A. and C. Lustig, *Brain aging: reorganizing discoveries about the aging mind.* Curr Opin Neurobiol, 2005. **15**(2): p. 245-51.
13. Reuter-Lorenz, P.A. and D.C. Park, *How does it STAC up? Revisiting the scaffolding theory of aging and cognition.* Neuropsychol Rev, 2014. **24**(3): p. 355-70.
14. Nyberg, L., et al., *Memory aging and brain maintenance.* Trends Cogn Sci, 2012. **16**(5): p. 292-305.
15. Mowinckel, A.M., T. Espeseth, and L.T. Westlye, *Network-specific effects of age and in-scanner subject motion: a resting-state fMRI study of 238 healthy adults.* Neuroimage, 2012. **63**(3): p. 1364-73.
16. Stumme, J., et al., *Functional network reorganization in older adults: Graph-theoretical analyses of age, cognition and sex.* Neuroimage, 2020. **214**: p. 116756.
17. Bittner, N., et al., *Combining lifestyle risks to disentangle brain structure and functional connectivity differences in older adults.* Nature communications, 2019. **10**(1): p. 1-13.
18. Hamer, M. and G.D. Batty, *Association of body mass index and waist-to-hip ratio with brain structure: UK Biobank study.* Neurology, 2019. **92**(6): p. e594-e600.
19. Caspers, S., et al., *Pathway-specific genetic risk for Alzheimer's disease differentiates regional patterns of cortical atrophy in older adults.* Cerebral Cortex, 2020. **30**(2): p. 801-811.
20. Nussbaum, R., et al., *Associations of Air Pollution and Noise with Local Brain Structure in a Cohort of Older Adults.* Environ Health Perspect, 2020. **128**(6): p. 67012.
21. Karama, S., et al., *Cigarette smoking and thinning of the brain's cortex.* Mol Psychiatry, 2015. **20**(6): p. 778-85.
22. Sperling, R.A., et al., *Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease.* Alzheimers Dement, 2011. **7**(3): p. 280-92.
23. McGuinness, B., et al., *Predicting conversion to dementia in a memory clinic: A standard clinical approach compared with an empirically defined clustering method (latent profile analysis) for mild cognitive impairment subtyping.* Alzheimers Dement (Amst), 2015. **1**(4): p. 447-54.
24. Jessen, F., et al., *The characterisation of subjective cognitive decline.* Lancet Neurol, 2020. **19**(3): p. 271-278.
25. Zilles, K. and K. Amunts, *Individual variability is not noise.* Trends Cogn Sci, 2013. **17**(4): p. 153-5.
26. Caspers, S., et al., *Studying variability in human brain aging in a population-based German cohort-rationale and design of 1000BRAINS.* Frontiers in aging neuroscience, 2014. **6**: p. 149.
27. Kalbe, E., et al., *DemTect: a new, sensitive cognitive screening test to support the diagnosis of mild cognitive impairment and early dementia.* Int J Geriatr Psychiatry, 2004. **19**(2): p. 136-43.
28. Stumme, J., et al., *Functional network reorganization in older adults: Graph-theoretical analyses of age, cognition and sex.* NeuroImage, 2020: p. 116756.

29. Jockwitz, C., et al., *Age-and function-related regional changes in cortical folding of the default mode network in older adults.* Brain Structure and Function, 2017. **222**(1): p. 83-99.
30. Ainsworth, B.E., et al., *2011 Compendium of Physical Activities: a second update of codes and MET values.* Med Sci Sports Exerc, 2011. **43**(8): p. 1575-81.
31. Kivipelto, M., F. Mangialasche, and T. Ngandu, *Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease.* Nat Rev Neurol, 2018. **14**(11): p. 653-666.
32. Wahl, D., et al., *Aging, lifestyle and dementia.* Neurobiol Dis, 2019. **130**: p. 104481.
33. McDonough, I.M. and R.S. Allen, *Biological markers of aging and mental health: A seed and soil model of neurocognitive disorders.* Aging Ment Health, 2019. **23**(7): p. 793-799.
34. Suzuki, H., et al., *Associations of Regional Brain Structural Differences With Aging, Modifiable Risk Factors for Dementia, and Cognitive Performance.* JAMA Netw Open, 2019. **2**(12): p. e1917257.
35. Poulakis, K., et al., *Heterogeneous patterns of brain atrophy in Alzheimer's disease.* Neurobiol Aging, 2018. **65**: p. 98-108.
36. Franke, K. and C. Gaser, *Longitudinal Changes in Individual BrainAGE in Healthy Aging, Mild Cognitive Impairment, and Alzheimer's Disease.* GeroPsych, 2012. **25**(4): p. 235-245.
37. Franke, K. and C. Gaser, *Ten Years of BrainAGE as a Neuroimaging Biomarker of Brain Aging: What Insights Have We Gained?* Front Neurol, 2019. **10**: p. 789.
38. Amunts, K., Mohlberg, H., Bludau, S., Zilles, K., *Julich-Brain: A 3D probabilistic atlas of the human brain's cytoarchitecture.* Science, 2020. **369**: p. 988-992.
39. Caspers, S., et al., *The human inferior parietal lobule in stereotaxic space.* Brain Struct Funct, 2008. **212**(6): p. 481-95.
40. Caspers, S., et al., *The human inferior parietal cortex: cytoarchitectonic parcellation and interindividual variability.* Neuroimage, 2006. **33**(2): p. 430-48.
41. Amunts, K., et al., *Broca's region revisited: cytoarchitecture and intersubject variability.* J Comp Neurol, 1999. **412**(2): p. 319-41.
42. Geyer, S., et al., *Areas 3a, 3b, and 1 of human primary somatosensory cortex. Part 2. Spatial normalization to standard anatomical space.* Neuroimage, 2000. **11**(6 Pt 1): p. 684-96.
43. Geyer, S., A. Schleicher, and K. Zilles, *Areas 3a, 3b, and 1 of human primary somatosensory cortex.* Neuroimage, 1999. **10**(1): p. 63-83.
44. Caspers, S., et al., *Organization of the human inferior parietal lobule based on receptor architectonics.* Cereb Cortex, 2013. **23**(3): p. 615-28.
45. Amunts, K., et al., *Broca's region: novel organizational principles and multiple receptor mapping.* PLoS Biol, 2010. **8**(9).
46. Bludau, S., et al., *Integration of transcriptomic and cytoarchitectonic data implicates a role for MAOA and TAC1 in the limbic-cortical network.* Brain Struct Funct, 2018. **223**(5): p. 2335-2342.
47. Pinho, A.L., et al., *Individual Brain Charting, a high-resolution fMRI dataset for cognitive mapping.* Sci Data, 2018. **5**: p. 180105.
48. Hahn, C. and C.U. Lee, *A Brief Review of Paradigm Shifts in Prevention of Alzheimer's Disease: From Cognitive Reserve to Precision Medicine.* Front Psychiatry, 2019. **10**: p. 786.

49. Lauschke, V.M., Y. Zhou, and M. Ingelman-Sundberg, *Novel genetic and epigenetic factors of importance for inter-individual differences in drug disposition, response and toxicity.* Pharmacol Ther, 2019. **197**: p. 122-152.
50. Amunts, K., et al., *The Human Brain Project-Synergy between neuroscience, computing, informatics, and brain-inspired technologies.* PLoS Biol, 2019. **17**(7): p. e3000344.
51. Zilles, K. and K. Amunts, *Receptor mapping: architecture of the human cerebral cortex.* Curr Opin Neurol, 2009. **22**(4): p. 331-9.
52. Goulas, A., et al., *The natural axis of transmitter receptor distribution in the human cerebral cortex.* bioRxiv, 2020.
53. Belloy, M.E., V. Napolioni, and M.D. Greicius, *A Quarter Century of APOE and Alzheimer's Disease: Progress to Date and the Path Forward.* Neuron, 2019. **101**(5): p. 820-838.
54. El Houssaini, K., C. Bernard, and V.K. Jirsa, *The Epileptor Model: A Systematic Mathematical Analysis Linked to the Dynamics of Seizures, Refractory Status Epilepticus, and Depolarization Block.* eNeuro, 2020. **7**(2).
55. Jirsa, V.K., et al., *The Virtual Epileptic Patient: Individualized whole-brain models of epilepsy spread.* Neuroimage, 2017. **145**(Pt B): p. 377-388.
56. Proix, T., et al., *Individual brain structure and modelling predict seizure propagation.* Brain, 2017. **140**(3): p. 641-654.
57. Reitz, C., *Toward precision medicine in Alzheimer's disease.* Ann Transl Med, 2016. **4**(6): p. 107.
58. Zimmermann, J., et al., *Differentiation of Alzheimer's disease based on local and global parameters in personalized Virtual Brain models.* Neuroimage Clin, 2018. **19**: p. 240-251.
59. Cirillo, D. and A. Valencia, *Big data analytics for personalized medicine.* Curr Opin Biotechnol, 2019. **58**: p. 161-167.
60. Schulz, M.A., et al., *Different scaling of linear models and deep learning in UKBiobank brain images versus machine-learning datasets.* Nat Commun, 2020. **11**(1): p. 4238.
61. Einevoll, G.T., et al., *The Scientific Case for Brain Simulations.* Neuron, 2019. **102**(4): p. 735-744.
62. Stefanovski, L., et al., *Linking Molecular Pathways and Large-Scale Computational Modeling to Assess Candidate Disease Mechanisms and Pharmacodynamics in Alzheimer's Disease.* Front Comput Neurosci, 2019. **13**: p. 54.