Genome-wide methylation study of wellbeing in discordant monozygotic twins

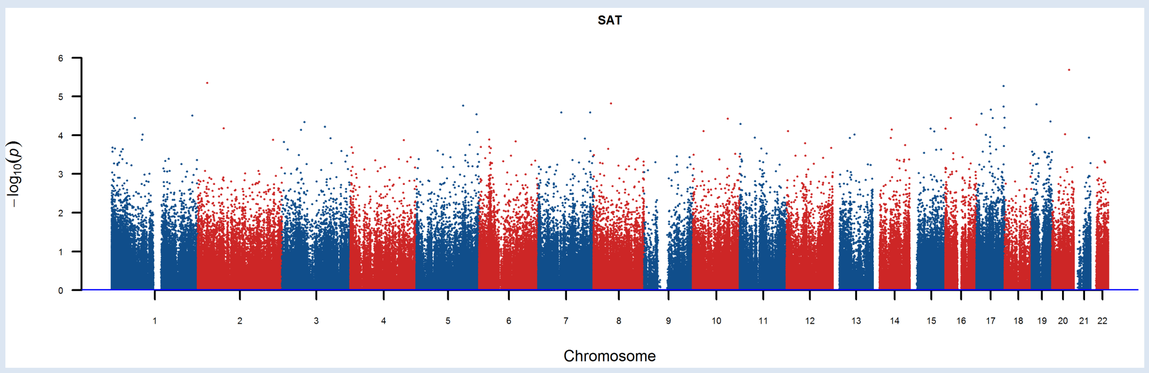
Bart M. L. Baselmans*, Rosanne S. van der Deijl*, Jenny van Dongen, BIOS Consortium, Dorret I. Boomsma, and Meike Bartels

Motivation

Wellbeing (WB) is a major topic of interest in many scientific disciplines. While the importance of the interplay between genes and environment has been well recognized in complex traits, most studies on wellbeing have only investigated genetic and environmental components separately. Recently, the first epigenome-wide association study (EWAS) for WB found two CpG sites for which methylation levels were genome-wide significantly associated with WB after Bonferroni correction[1]. To further investigate wellbeing-associated differences in methylation, a discordant monozygotic (MZ) twin model is a powerful design, since MZ twins are matched for a range of possible confounding factors, including genetic make-up, age, gender, and many environmental influences, due to shared upbringing.

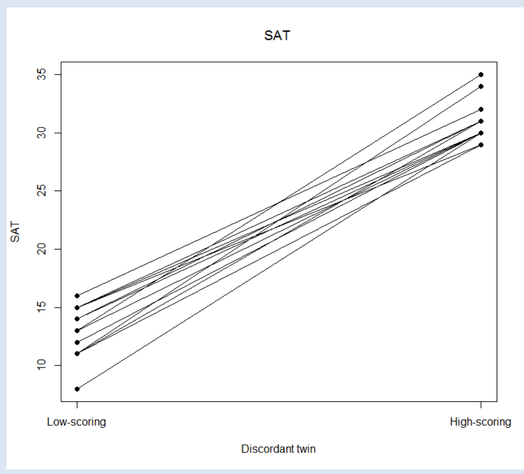
This study

We conducted an EWAS in 14 monozygotic (MZ) twins discordant for Satisfaction with Life (SAT) score. None of the probes reached genome-wide significance after Bonferroni correction. However, we identified numerous differentially methylated regions associated with SAT. These loci there were not differentially methylated in SAT-concordant twins.



Methods

Sample
Participants were selected from longitudinal studies and the biobank project performed by the Netherlands Twin Register (NTR). WB was measured with the SAT scale. For each subject we selected SAT scores that were measured closest in time to the moment of blood draw. We considered twins as discordant for wellbeing when this score was 16 or lower (equivalent to a 5 or 'insufficient' on the Quality of Life scale) and the co-twin score was 28 or higher (equivalent to a 7 or 'sufficient' on the QoL scale). This method classified 14 MZ twin pairs as discordant for SAT.



Analyses
DNA methylation was measured with the Infinium Human-Methylation450 BeadChip Kit. To test for differences in methylation within twin pairs, we performed paired t-tests on each probe. The outcome variables for these tests were the residual methylation levels, which were calculated from the initial β levels by adjusting them many covariates including different blood cell counts, age and smoking.

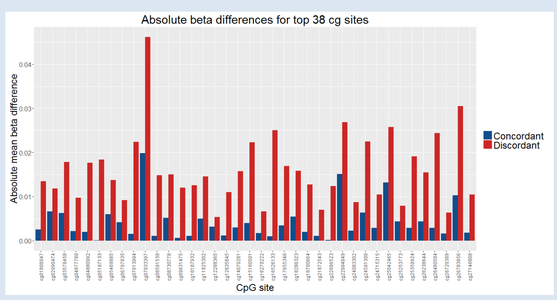
Results

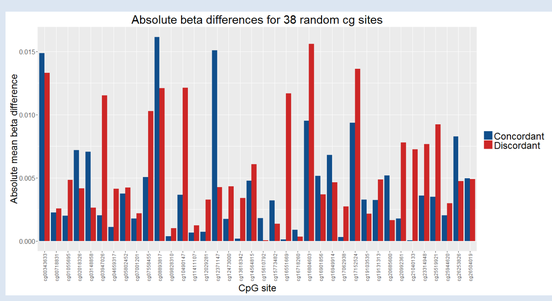
Site-specific wellbeing-related methylation differences
While none of our probes showed genome-wide significance after Bonferroni correction, Δβ and p-values were in the range of similar study designs. Thirty-eight sites had a p-value $<1x10^{4}$, and three sites had a p-value $<1x10^{5}$.

Probe name	Δβ	p-value	Gene name	Chr.	Position
cg02990474	0.011802691	2.05546E-06	BCAS4	20	49416093
cg21872543	0.007015609	4.51825E-06	ZNF513	2	27603766
cg07833397	0.046176229	5.37044E-06	CBX4	17	77811499

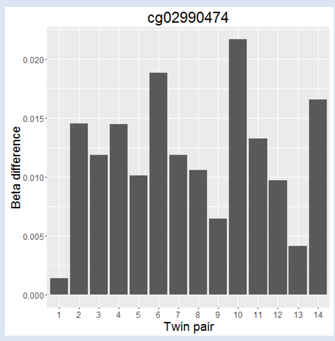
The closest genes for the top thirty-eight sites did not have obviously relevant functions or associations to the phenotype of well-being. However, all of these genes have found to be expressed in the brain. Two sites are of particular interest. First, cg08730778 (p = 3.65E-05) is located near the NDE1 gene, which encodes a protein that is essential for microtubule organization, mitosis, and neuronal migration. Second, cg25253773 (p = 6.74E-05) is located near the SEMA4F gene, playing a role in neural development.

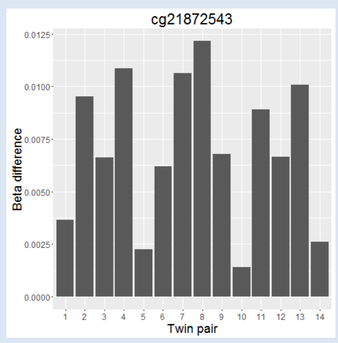
The 38 most significant probes ($p<1x10^{4}$) in discordant twins showed low Δβ in SAT-concordant twins. Moreover, in a random set of CpG sites we found no such differences in Δβ between discordant an concordant twins.

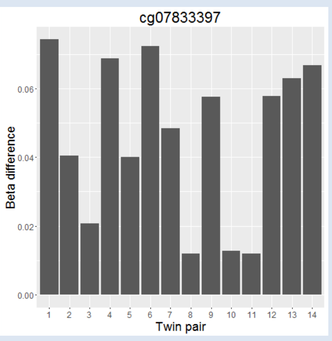




The top three most significant sites showed beta differences in the same direction for each twin pair (with the high-soring twin having higher beta levels than the low scoring twin).







Methylation variability
We found a highly significant difference in overall variance between the high- and low-scoring twins (p<2.2x10-16). Interestingly, while we found a higher variance in the high-scoring group ($\sigma^2 = 0.0010$) as compared to the low-scoring group ($\sigma^2 = 0.0009$), a number of EWAS studies on depression have found higher variation in depressed patients as compared to controls[2,3,4]. These findings may be explained by the hypothesis of differential susceptibility, which states that people differ in their susceptibility to the environment, rendering those more sensitive to negative experiences also more susceptible to positive experiences[5].

Conclusion

Our study highlights the role epigenetic alterations in the etiology of wellbeing. It also underlines the strength of the discordant twin design for epigenome-wide association studies.

[1]Baselmans, B. M. L., et al. (2015). Epigenome-wide association study of wellbeing. *Twin Res. & Hum. Genet* 18(6), 710–719.
[2]Dempster, E. L., et al. (2014). Genome-wide methylomic analysis of monozygotic twins discordant for adolescent depression. *Biol. Psychiat.*, 76(12), 977–983.
[3]Cordova-Palomera, A., et al. (2015). Genome-wide methylation study on depression. *Transl. Psychiat*, 5(4), e557.
[4]Byrne, E. M., et al. (2013). Monozygotic twins affected with major depressive disorder have greater variance in methylation than their unaffected co-twin. *Transl. Psychiat*, 3(6), e269.
[5]Belsky, J., & Pluess, M. (2009). Beyond diathesis stress: differential susceptibility to environmental influences. *Psychol. Bull.*, 135(6), 885.