

From: **Terrie Moffitt** <[tem11@duke.edu](mailto:tem11@duke.edu)>

Date: Thu, Jun 21, 2012 at 5:22 AM

Subject: GxE meta-analysis

To: Culverhouse@domain.invalid, Robert <[rculverh@dom.wustl.edu](mailto:rculverh@dom.wustl.edu)>, Alain Malafosse <[Alain.Malafosse@hcuge.ch](mailto:Alain.Malafosse@hcuge.ch)>, Alessandro Serretti <[alessandro.serretti@unibo.it](mailto:alessandro.serretti@unibo.it)>, Avshalom Caspi <[avshalom.caspi@duke.edu](mailto:avshalom.caspi@duke.edu)>, Bekh Bradley <[rbradl2@emory.edu](mailto:rbradl2@emory.edu)>, "[Bill.Deakin@manchester.ac.uk](mailto:Bill.Deakin@manchester.ac.uk)" <[Bill.Deakin@manchester.ac.uk](mailto:Bill.Deakin@manchester.ac.uk)>, Blanca Gutiérrez <[blancag@ugr.es](mailto:blancag@ugr.es)>, "[c.m.middeldorp@vu.nl](mailto:c.m.middeldorp@vu.nl)" <[c.m.middeldorp@vu.nl](mailto:c.m.middeldorp@vu.nl)>, Cecilia Aslund <[cecilia.aslund@gmail.com](mailto:cecilia.aslund@gmail.com)>, "[chorbovv@WUSTL.EDU](mailto:chorbovv@WUSTL.EDU)" <[chorbovv@wustl.edu](mailto:chorbovv@wustl.edu)>, Christian Otte <[Christian.Otte@charite.de](mailto:Christian.Otte@charite.de)>, Christian Schwahn <[schwahn@uni-greifswald.de](mailto:schwahn@uni-greifswald.de)>, "[coventrywill@gmail.com](mailto:coventrywill@gmail.com)" <[coventrywill@gmail.com](mailto:coventrywill@gmail.com)>, Dana Gleib <[danaglei@sonic.net](mailto:danaglei@sonic.net)>, "[ebinder@emory.edu](mailto:ebinder@emory.edu)" <[ebinder@emory.edu](mailto:ebinder@emory.edu)>, "Eley, Thalia" <[thalia.eley@kcl.ac.uk](mailto:thalia.eley@kcl.ac.uk)>, "[Enda.Byrne@qimr.edu.au](mailto:Enda.Byrne@qimr.edu.au)" <[Enda.Byrne@qimr.edu.au](mailto:Enda.Byrne@qimr.edu.au)>, Frank Bellivier <[frank.bellivier@inserm.fr](mailto:frank.bellivier@inserm.fr)>, "[Gabriella.Juhasz@manchester.ac.uk](mailto:Gabriella.Juhasz@manchester.ac.uk)" <[Gabriella.Juhasz@manchester.ac.uk](mailto:Gabriella.Juhasz@manchester.ac.uk)>, György Bagdy <[bag13638@iif.hu](mailto:bag13638@iif.hu)>, "Habersti@Colorado.edu" <[Habersti@colorado.edu](mailto:Habersti@colorado.edu)>, Hans Grabe <[grabeh@uni-greifswald.de](mailto:grabeh@uni-greifswald.de)>, Hiroshi Sato ??? <[satohiroshi@kwansei.ac.jp](mailto:satohiroshi@kwansei.ac.jp)>, "[Holzman@epi.msu.edu](mailto:Holzman@epi.msu.edu)" <[Holzman@epi.msu.edu](mailto:Holzman@epi.msu.edu)>, "Ian H. Gotlib" <[ian.gotlib@stanford.edu](mailto:ian.gotlib@stanford.edu)>, Isabelle Jaussent <[isabelle.jaussent@inserm.fr](mailto:isabelle.jaussent@inserm.fr)>, "[jeanette.scheid@ht.msu.edu](mailto:jeanette.scheid@ht.msu.edu)" <[jeanette.scheid@ht.msu.edu](mailto:jeanette.scheid@ht.msu.edu)>, John Nurnberger <[jnurnber@iupui.edu](mailto:jnurnber@iupui.edu)>, "John.Hewitt@Colorado.edu" <[John.Hewitt@colorado.edu](mailto:John.Hewitt@colorado.edu)>, Jorge Cervilla <[jacb@ugr.es](mailto:jacb@ugr.es)>, Judit Lazary <[lazaryjudit@yahoo.com](mailto:lazaryjudit@yahoo.com)>, Karen Ritchie <[karen.ritchie@inserm.fr](mailto:karen.ritchie@inserm.fr)>, "[kbutze@emory.edu](mailto:kbutze@emory.edu)" <[kbutze@emory.edu](mailto:kbutze@emory.edu)>, Kent Nilsson <[kent.nilsson@ltv.se](mailto:kent.nilsson@ltv.se)>, "Bierut, Laura" <[bierutl@psychiatry.wustl.edu](mailto:bierutl@psychiatry.wustl.edu)>, Laura Mandelli <[laura.mandelli@unibo.it](mailto:laura.mandelli@unibo.it)>, "[Marcus.Munafo@bris.ac.uk](mailto:Marcus.Munafo@bris.ac.uk)" <[Marcus.Munafo@bris.ac.uk](mailto:Marcus.Munafo@bris.ac.uk)>, Margit Burmeister <[margit@umich.edu](mailto:margit@umich.edu)>, "[Mary.Whooley@va.gov](mailto:Mary.Whooley@va.gov)" <[Mary.Whooley@va.gov](mailto:Mary.Whooley@va.gov)>, Maxine Weinstein <[weinstma@georgetown.edu](mailto:weinstma@georgetown.edu)>, Naomi Breslau <[breslau@epi.msu.edu](mailto:breslau@epi.msu.edu)>, "[naomi.wray@uq.edu.au](mailto:naomi.wray@uq.edu.au)" <[naomi.wray@uq.edu.au](mailto:naomi.wray@uq.edu.au)>, Nick Martin <[Nick.Martin@qimr.edu.au](mailto:Nick.Martin@qimr.edu.au)>, Nicole Jones <[Nicole.Jones@hc.msu.edu](mailto:Nicole.Jones@hc.msu.edu)>, Noreen Goldman <[ngoldman@opr.princeton.edu](mailto:ngoldman@opr.princeton.edu)>, "[nwjwainwright@btinternet.com](mailto:nwjwainwright@btinternet.com)" <[nwjwainwright@btinternet.com](mailto:nwjwainwright@btinternet.com)>, Paul Surtees <[ps404@cam.ac.uk](mailto:ps404@cam.ac.uk)>, Philippe Courtet <[philippe.courtet@univ-montpl.fr](mailto:philippe.courtet@univ-montpl.fr)>, "Ressler, Kerry" <[kressle@emory.edu](mailto:kressle@emory.edu)>, Ricardo Araya <[r.araya@bris.ac.uk](mailto:r.araya@bris.ac.uk)>, Rob Culverhouse <[rculverh@wustl.edu](mailto:rculverh@wustl.edu)>, Robert Zucker <[zuckerra@umich.edu](mailto:zuckerra@umich.edu)>, Sandra Villafuerte <[svillafu@umich.edu](mailto:svillafu@umich.edu)>, Srijan Sen <[srijan@umich.edu](mailto:srijan@umich.edu)>, "[terrie.moffitt@duke.edu](mailto:terrie.moffitt@duke.edu)" <[terrie.moffitt@duke.edu](mailto:terrie.moffitt@duke.edu)>, "[TODOROV@WUSTL.EDU](mailto:TODOROV@WUSTL.EDU)" <[TODOROV@wustl.edu](mailto:TODOROV@wustl.edu)>, William Coventry <[William.Coventry@qimr.edu.au](mailto:William.Coventry@qimr.edu.au)>, Albertine Oldehinkel <[a.j.oldehinkel@umcg.nl](mailto:a.j.oldehinkel@umcg.nl)>, Esther Nederhof <[e.nederhof@umcg.nl](mailto:e.nederhof@umcg.nl)>, Johan Ormel <[j.ormel@umcg.nl](mailto:j.ormel@umcg.nl)>, George Patton <[george.patton@rch.org.au](mailto:george.patton@rch.org.au)>, Graig Olsson <[craig.olsson@rch.org.au](mailto:craig.olsson@rch.org.au)>, Christina O'Loughlin <[christina.oloughlin@mcri.edu.au](mailto:christina.oloughlin@mcri.edu.au)>, Katharina Domschke <[Domschke\\_K@klinik.uni-wuerzburg.de](mailto:Domschke_K@klinik.uni-wuerzburg.de)>, Peter McGuffin <[peter.mcguiffin@kcl.ac.uk](mailto:peter.mcguiffin@kcl.ac.uk)>, Simon Easteal <[Simon.Easteal@anu.edu.au](mailto:Simon.Easteal@anu.edu.au)>, Sarah Cohen-Woods <[sarah.cohen-woods@kcl.ac.uk](mailto:sarah.cohen-woods@kcl.ac.uk)>, Helen Fisher <[helen.2.fisher@kcl.ac.uk](mailto:helen.2.fisher@kcl.ac.uk)>, Anne Farmer <[anne.farmer@kcl.ac.uk](mailto:anne.farmer@kcl.ac.uk)>, Marco Sarchiapone <[marco.sarchiapone@me.com](mailto:marco.sarchiapone@me.com)>, Nicholas Stefanis <[nistefan@med.uoa.gr](mailto:nistefan@med.uoa.gr)>, "Saccone, Nancy" <[nlims@genetics.wustl.edu](mailto:nlims@genetics.wustl.edu)>, Kaarin Anstey <[kaarin.anstey@anu.edu.au](mailto:kaarin.anstey@anu.edu.au)>

Dear Dr. Culverhouse,

Thank you for the courtesy of sharing your research plan for the meta-analysis of the stress and depression GxE literature. You've accomplished a lot of work!

As you know, I have left it to my collaborator Avshalom Caspi to communicate with you on behalf of our team, and he has previously written to you a couple of months ago to express our concerns, which were sufficient to lead us to withdraw from the project .

At this point, I hope you will indulge me if I make one last effort, for the record, to express two remaining concerns with the plan.

I do not agree with your plan to study lifetime depression as an outcome measure. The literature documenting that retrospective recall of lifetime depression is inadequate for research purposes has been reviewed in my 2010 paper in Psychological Medicine. Setting aside for the moment the inadequate quality of lifetime depression reports, the main reason that this measure should not be used in your analyses is that a lifetime measure precludes establishing temporal order between the hypothesized cause and the hypothesized effect. To test the hypothesis that individuals with an at-risk serotonin transporter genotype develop depression AFTER and IN RESPONSE to life stress, a minimal criterion for a valid test is a set of measures that can unambiguously establish that the stress came before the depression. One cannot simply make the assumption that depression follows stress, because there is a literature showing that individuals with depression tend to experience more stressful life events as a consequence of their mood, for example, depressed individuals have more domestic violence and are more likely to become divorced. To use retrospective reports of lifetime depression is tantamount to using lifetime weight to test hypotheses about the cause of low birth-weight, or to use lifetime IQ to test hypotheses about causes of cognitive decline in Alzheimers dementia; the measure sounds kinda the same, but it is not. Timing is everything. This point is not new; we addressed the point empirically in our original 2003 Science paper. We already showed in that paper empirically that unless the stress comes before the depression, the GxE finding is not obtained. The point is also explained very clearly in a nice powerpoint lecture "What Do Survey Data Really Mean? Considering Issues of Causality and Temporality in Survey Research," by Seth Noar, PhD, University of North Carolina, which can be found here:

<http://www.nidcr.nih.gov/Research/DER/BSSRB/PowerPointPresentations/default.htm>.

I also do not agree with your plan to limit the data sets to those with a minimum sample size of 500 participants. Your project is not discovery science, it is hypothesis testing science. Discovery science requires large samples, but hypothesis testing does not. In hypothesis-testing

science, the consideration of sample size is secondary to more primary considerations of quality of the measures and correctness of design. Many of the most ideally designed studies for testing this hypothesis have samples under 500. In particular, studies of medical illness stressors tend to be small, but well designed, and it is unfortunate that your plan excludes them. The over-emphasis in your plan on sample size, coupled with exclusion of many well-designed studies for testing the hypothesis, is misguided. It seems that you have first decided what data sets you wish to include, and then bent the hypothesis test to fit the measures in those data sets, when in fact hypothesis testing is properly conducted the other way around. Some studies you intend to include, no matter how large, must be designated unsuitable for this project if their measures of stress and depression are weak, and if their designs do not allow establishing clear temporal order between hypothetical cause and outcome. Again, this point is not new. Avshalom and I have explained it in our 2010 American J of Psychiatry paper, Uher et al have explained it in two publications, and Karg et al have also explained it in their meta-analysis.

Given that these two (and other) issues are not new to our field, these methodological mistakes have been made often before, and they have been repeatedly pointed out before in published articles, your plan to me seems to be going back 10 years, offering the same old methodological weaknesses, and no real improvement. I am not sure why an editor would be interested in publishing another paper on this hypothesis that uses methodologies that everyone knows are inappropriate. Maybe the sheer big N will attract editorial favor, but that seems pretty cheap science to me. What a missed opportunity to do something better.

Yours, Terrie Moffitt

--

Terrie E Moffitt

[WWW.MOFFITTCASPI.COM](http://WWW.MOFFITTCASPI.COM)

Web of Knowledge Researcher ID = D-5295-2011

Knut Schmidt Nielsen Professor, Departments of Psychology and Neuroscience, Psychiatry and Behavioral Sciences, and Institute for Genome Sciences and Policy. Suite 201 Grey House, 2020 West Main Street, Duke University Box 104410, Durham, NC 27708, USA. Tel. 001 [919-684-6679](tel:919-684-6679), Fax 001 [919-684-5912](tel:919-684-5912)

Professor of Social Behaviour and Development, Social, Genetic and Developmental Psychiatry Centre, P080, Institute of Psychiatry, De Crespigny Park, London, SE5 8AF United Kingdom. Tel. 0044 [207 848 0936](tel:207-848-0936), Fax 0044 [207 848 5262](tel:207-848-5262)

Associate Director, Dunedin Multidisciplinary Health and Development Research Unit, PO Box 913, Dunedin School of Medicine, Dunedin, New Zealand. Tel. 0064 3 479 8508, Fax 0064 3 479 5487.