Email

Manuscript #	JN-RM-4402-15
Title	Large-scale meta-analysis of human medial frontal cortex reveals tripartite functional organization
Corresponding Author	Mr. Alejandro I De La Vega (University of Colorado at Boulder)
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To:	delavega@colorado.edu
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Subject:	Decision on Journal of Neuroscience JN-RM-4402-15
	4th Jan 2016 Dear Mr. De La Vega: Your Reviewing Editor, Chris Baker, and I have received the reviews of your paper, "Large-scale meta-analysis of human medial frontal cortex reveals tripartite functional organization" (JN-RM-4402-15). Although the referees feel that these results are of potential interest, they have raised a number of substantive concerns, which preclude publication of the paper in the Journal of Neuroscience, at least in its present form. The reviews are appended to this email. We hope that you will be able to address the referees' concerns in full and resubmit the manuscript, along with a point-by-point reply to the reviews that indicates your response to each concern. Before we make a decision about publication, we will have your revision re-reviewed by the reviewers. NOTE: in the revision, please add journal's name, issue, and pages, in lines 534-5. And fix similar omissions in many other places in the reference section. Your revision must include the manuscript with new text indicated in a bold or colored font. You should scrutinize your paper at this time for any corrections in style or substance that you wish to make. In the event that your revision is accepted, you will not be allowed to make style or content changes at the proof stage. Your submission must also include publication-quality figures, each in a separate EPS or TIFF (300 dpi) file. Please make sure your figures adhere to Journal style requirements to avoid delays in manuscript processing. Detailed guidelines for figures are available here: http://www.jneurosci.org/site/misc/ifa_illustrations.xhtml#Figures When uploading the revised manuscript, there is a link available for the corresponding author to complete the electronic License to Publish form. A link to the form will also be available on the author's home page at http://jneurosci.msubmit.net if not completed at time of submission. Please return your revision within three months of this decision. If you need more time, please contact our central office (jn@sfn.org). A checklist for submitting a revision is available here:

http://www.jneurosci.org/site/misc/JN_Revised_Submissions_Checklist.pdf. When you are ready to submit your revision, you can log in using the link below and open the "Post Decision" folder. Click on the manuscript number to see the link to create your revision. If the link is gone, please contact our central office (jn@sfn.org).

Link Not Available

Yours sincerely,

Yavin Shaham
Senior Editor
Journal of Neuroscience

Manuscript Instructions

- The sex of the species studied is not mentioned in the materials and methods section. Please mention "male", "female", "x males and x females", "of either sex".

Reviewer #1 (Rationale for Significance Rating (Required)):

The MFC plays a central role in contemporary models of emotion, pain, and cognitive control. Work in these domains has, in turn, profoundly influenced contemporary perspectives on more complex phenomena, including social cognition and a variety of neuropsychiatric disorders. Yet, the architecture and significance of activity in the MFC remains enigmatic. This study--which provides a comprehensive functional map of the human MFC--is conceptually significant and methodologically innovative, and it will likely serve as a template for future efforts to understand the functional architecture and significance of other regions of association cortex.

Reviewer #1 :

##########################
JN-RM-4402-15
Large-scale meta-analysis of human medial frontal cortex reveals tripartite functional organization
Alejandro De La Vega, University of Colorado at Boulder
Luke Chang, Dartmouth College
Marie Banich, University of Colorado at Boulder
Tor Wager, University of Colorado
Tal Yarkoni, UT Austin
##########################
SUMMARY
The MFC plays a central role in contemporary models of emotion, pain, and

cognitive control. Work in these basic domains has, in turn, profoundly influenced contemporary perspectives on more complex phenomena, including social cognition and a variety of neuropsychiatric disorders. Despite this progress, the functional architecture and significance of activity in the MFC remains incompletely understood. Thus, the focus of this MS is timely, important, and likely to be of keen interest to a broad spectrum of basic and clinical researchers.

Key strengths include:
a) comprehensive scope of the analysis, in terms of the sheer number of studies, the number of psychological domains, and the size of the ROI (MFC rather than say sgACC or area 32')

b) topic modeling; this markedly enhances the value of Neurosynth

c) thoughtful, unbiased approach to reducing dimensionality

d) authors report multiple scales (3/coarse vs 9/fine meta-analytically defined sub-divisions of MFC

e) machine learning approach (naive Bayes classifier) to identifying psychological profiles for these sub-divisions

In short, the work reported in this MS logically builds this group's prior successes, it is conceptually significant and methodologically innovative, and it will likely serve as a template for future efforts to understand the functional architecture and significance of other regions of association cortex (e.g. insula, lateral PFC, PPC).

In the section that follows, I provide a few suggestions for further strengthening this important report.

Signed,
AJ Shackman

MAJOR / GENERAL
1. INTRODUCTION: Describe what the author(s) hoped to achieve accurately and clearly state the problem being investigated? Establish how the current manuscript builds on extant work (including recent work) and how the current manuscript will make a novel contribution. Provide a specific rationale for the main variables?

a. Yes, but could use a little polish; see my specific comments below

b. The rationale for partitioning MFC on the basis of meta-analytic co-activation is inadequate, given that this is the central means of identifying the parcels for subsequent profiling

2. METHOD: Are the claims convincing? If not, what further evidence is needed? Are the constructs adequately operationalized? Is the design suitable for addressing the aims? Sufficient information to permit replication? Are the methods ordered in a thoughtful way?

a. Yes, but at times the complex methodology is challenging to follow. Specifically, the terminology is unwieldy at points (voxels, features, parcels, zones, sub-regions, and ROI's); be consistent.

b. Figure 1 is incredibly helpful, yet, is not cited in the text. It would be helpful to liberally cite each panel as you work your way thru the constituent methods

c. Not clear whether co-activation is w/in or b/w studies. If between, why?

3. ANALYTIC STRATEGY: Statistics need to be clearly justified and explained, and appropriate for testing the hypotheses (i.e., do the tests fit the stated aims and claims?).

a. Very appropriate, but need to be more clearly explained.

4. RESULTS: Clearly laid out and in a logical sequence, typically flowing from the aims. Extended interpretation of results should not be included in this section, but brief summaries and contextual information is often helpful.

a. OK. Figures are brilliant.

5. DISCUSSION / IMPLICATIONS: Puts the findings in the context of prior literature, acknowledge limitations of the current study, and suggest specific implications for future research and potential applications. Are the claims supported by the results? Have the authors indicated how the results relate to expectations and to earlier research and theory? Does the conclusion explain how the research has moved the body of scientific knowledge forward?

a. The Discussion needs work. At times, the authors fall prey to over-selling the novelty and significance of their results. The results themselves are genuinely interesting and exciting, so there is no reason to exaggerate differences with prior research or to over-interpret the theoretical significance.

b. At times, the literature cited in the first half of the Discussion seemed dated

c. The limitations section needs work. Careful scrutiny suggests that these are not necessarily the most important limitations and the most important avenues for future research.

d. This study is significant, but the theoretical and translational implications of the work are not clearly outlined in the Discussion.

6. FIGURES: Should be high quality and visually depict the most important results.

a. Good; see detailed comments below

7. TITLE: Clearly describe the article?

a. OK. Tripartite is all the rage these days (cf. http://shackmanlab.org/wp-content/uploads/2015/07/fox_shackman_pnas2015.pdf)

8. ABSTRACT: Adequately represent the content of the paper and generate suitable excitement? Does it convey or mislead the reader about the the implications / limitations?

a. Good; see detailed comments below

9. DETAILED ASSESSMENT OF METHOD & ANALYTIC STRATEGY / REPORTING

- If applicable, is the method used for randomization to groups clear? How

well were the groups matched?

n/a

- Are the sex/age and other key demographics of the subjects in each group reported?

n/a

- If applicable, is a statement of the extent to which investigator knew the group allocation during the experiment and in assessing outcome included ("blinding")?

n/a

- Are statistical or technical criteria for excluding, rejecting, or censoring data points reported?

n/a

- Are the criteria for determining the sample size (given attrition) clearly articulated?

n/a

- Is the task clearly described?

n/a

- For each result reported in the text, tables, or figures, are the following clear?: The test coefficient, N, p (1- or 2-sided), df, any descriptive statistics, clearly defined error bars as applicable.

ok

- Are statistical tests justified and clearly defined for every reported result? If applicable, are nuisance variates clearly articulated?

ok

- Do the data meet the assumptions of the specific statistical test (e.g. normality, equal variances)?

ok

- Are there appropriate adjustments for multiple comparisons?

yes

- If applicable, is any custom software or scripts clearly described? If computer code was used to generate results that are central to the paper's conclusions, do the authors include a statement to indicate whether and how the code can be accessed (include version information as necessary and any restrictions on availability).

yes

For brain imaging papers

- Is the coordinate space for the anatomical/functional imaging data clearly defined as subject/native space or standardized stereotaxic space, e.g., original Talairach, MNI305, ICBM152, etc?

no; should mention in one sent

- If there was data normalization/standardization to a specific space template, is the type of transformation (linear vs. nonlinear) used and image types being transformed clearly described?

n/a

- How were anatomical locations determined, e.g., via an automated labeling algorithm (AAL), standardized coordinate database (Talairach daemon), probabilistic atlases, etc.?

needs to be clarified; see my detailed comments

- Are the results or threshold based on an ROI (region of interest) analysis? If so, is the rationale clearly described? How were the ROI's defined (functional vs anatomical localization)?

n/a

MINOR / SPECIFIC
- "The medial frontal cortex (MFC) encompasses many functionally distinct foci that have been
54 associated with a wide variety of cognitive states using functional neuroimaging."

launching right in to a laundry list w/ no figure make this a little tough to digest -- give me a little time to warm up; might be better to say roughtly what it is/where it is, that it is anatomically and functionally heterogeneous; then outline regions; and then describe some key associations.....or start by saying that it plays a key role in contemporary models of emotion, cognition, and pain, yet the functional organization/architecture and significance remain unclear AND THEN start to break it down. a figure would help.

- "The medial frontal cortex (MFC) encompasses many functionally distinct foci that have been
54 associated with a wide variety of cognitive states using functional neuroimaging"

aside - note that in your laundry list, you go on to describe evidence that is not 'cognitive' and not based on 'imaging'

- "Since most researchers tend to be intimately familiar with one
74 particular domain of cognition,"

i strongly agree, but would object to calling it 'cognition' ... maybe 'psychological domain, such as pain'

- "Since most researchers"
because

- "Such meta-analyses are further hampered by the limited
80 ability to draw conclusions about the relative specificity of brain activity to particular cognitive
81 processes- a limitation widely known as the reverse inference problem"

i strongly agree, but this was a little tough to digest (and will be even more difficult for readers not familiar w/ fwd vs reverse inference). maybe something like

'Furthermore, existing analyses, which have focused on the consistency of MFC activation in response to particular kinds of challenges (e.g. pain), cannot address the question of specificity'

or

'Furthermore, existing analyses, do not address the specificity of MFC activation. Specifically, they cannot address whether MFC activation is diagnostic of particular psychological states.'

or

'Furthermore, existing analyses, do not address the specificity of MFC activation. That is, they cannot address whether particular kinds of tasks preferentially recruit the MFC.' [here i was trying to steer clear of the concerns recently outlined by Yarkoni; http://www.talyarkoni.org/blog/2015/12/14/still-not-selective-comment-on-comment-on-comment-on-lieberman-eisenberger-2015/]

- "Here we attempt to overcome these issues"

Here we address these issues

- "Neurosynth, a diverse large-scale database of
87 over 10,000 fMRI studies."

Nsynth is more than a database, it's also a set of tools; you should clarify that it's an automated database; and you should cite something, either the URL or Tal's NM paper

- "and found that"
and show/demonstrate that

- "had a distinct pattern of psychological"

is marked/characterized by a distinct psychologcal profile

- "suggest that
100 previous studies may have overstated the case for the convergence of different processes in
101 MFC."

overstated the case seems to informal?

- "We analyzed the Neurosynth database (Yarkoni et al., 2011), a repository of 9,721 fMRI studies
108 and over 350,000 activations"

should provide data or DB version #; should clarify whether you were using the public side or the core tools

- "350,000 activations"

activation peaks/foci

- figure 1 is lovely, BUT there's no way of assessing the mesial-lateral 'depth' of the roi; i know it's a pain, but could add a tiny coronal or 3d image to panel A....or, at least remind the reader of the xyz bounds in the caption; and cite the figure in the text where you detail the roi

- "Moreover, the functional organization supporting these diverse
67 processes has been investigated using a wide range of methods, including cytoarchitecture
68 (Ongur and Price, 2000; Vogt, 2005), computational models (Alexander and Brown, 2011),
69 network-level descriptions (Andrews Hanna et al., 2010; Power et al., 2011), and theory-driven
70 meta-analyses (Bush et al., 2000; Shackman et al., 2011; Denny et al., 2012)."

it would be better to drop a few of the old refs (eg O&P'00 and Bush'00) and add in some non-imaging data eg electrophys from humans and or monkeys; this is reviewed in http://shackmanlab.org/wp-content/uploads/2014/05/cavanagh_shackman_JPP_2014.pdf among many other places

also, jess' last name is hyphenated

also, vogt '05 is superceded by vogt's 2008 paper w/ zilles group (or just cite his book)

- "less than 80"
fewer

- "We then calculated the correlation between each
122 MFC voxel"
need to unpack what you are correlating exactly, likelihood, normalized likelihood?

- "As this would
123 result in a very large matrix that would be computationally intractable to cluster, we"

To ensure that this was computationally tractable, we used spatial pca to ...

- "to reduce it to 100 components (100 voxels x 9721 studies)."

100 spatial comps (100 pseudo-voxels... or features

- "15259 x 100 feature"
15259 voxel x 100 featureS

- "selected the best output"

unpack best/inertia

- "is arguably an intractable problem"

there is no unique solution

- "We applied k-means clustering to this
130 matrix,"

you need to link this to the subsequent idea of 'parcels'

- "We clustered individual voxels inside of a MFC mask based on their co-activation with
116 voxels in the rest of the brain."

meta-analytic co-activation

- "To determine which voxels across the brain co-activated w 151 ith each MFC parcel, we
152 performed a meta-analysis resulting in whole-brain maps that indicate which voxels across the
153 brain are active in the studies that activated each parcel."

i'm confused; how is this different than the meta-analytic co-activation on page 7?

also, the terminology is starting to get unwieldy - voxels, features, parcels, zones, sub-regions, and ROI's; you need to clean this up and be consistent

- "To display the unique co-activation of
154 each region, we directly contrast co-activation patterns between zones and sub-regions within
155 each zone by performing a meta-analysis that contrasted studies that uniquely activated each ROI
156 to studies that activated other parcels in the same analysis (e.g. studies that activated anterior
157 MFC vs studies that activated middle and posterior MFC)."

In order to test/identify/assess, we ... -- not 'display'

how are 'zones' related to the earlier terms eg parcels?

- "performing a meta-analysis that contrasted studies that uniquely activated each ROI
156 to studies that activated other parcels in the same analysis (e.g. studies that activated anterior
157 MFC vs studies that activated middle and posterior MFC)."

when i 1st read this my comment was -- 'this is not really a meta per se, it seems more like a 'contrast' or a 'meta-analytic contrast' (like a moderator analysis in classic meta)'

but then i went and studied figure 1 and realized that (i think; could be wrong) that you are actually describing two steps at once, a meta and a meta contrast; you need to clarify this for the reader

- "For each voxel across the brain, we"

Email	More specifically, for ... - "calculated the conditional probability of activation across the selected set of studies" selected? do you mean the entire DB? in light of http://www.talyarkoni.org/blog/2015/12/14/still-not-selective-comment-on-comment-on-comment-on-lieberman-eisenberger-2015/, can you be more specific about this? you need to tread carefully here ; should probably temper 'unique' - "Next, we thresholded significant voxels using False Discovery Rate correction at p 161 < 0.01 and binarized the resulting maps for display." aren't you just saying you thresholded, doesn't that imply censoring subthresh vox? also, q not p - "We assessed our models' ability to predict if an uns 195 een study activated a region" awk wording; consider adding a parenthetical at the end defining this in terms of formal prob - "- because this measure is not detrimentally affected by unbalanced data (Jeni et al., 202 2013)." move this point into the nxt sent - "To generate functional specialization profiles" here you insert the additional adj 'specialization,' but given recent critical conversations in the blogosphere, might be better to either drop or use 'func preference profiles' - "defined as the 208 log of the ratio between the mean loading of each cognitive concept in studies that activated a 209 given region to the mean loading in studies that did not activate he ratio." typo; again, maybe add a parenthetical stating this in formal logic - fig 2 - why is it zones on the left and sub-regions on the right? also, is it really appropriate to label the yellow and green regions in the right panel as 'pre-SMA' (cf. http://shackmanlab.org/the-importance-of-respecting-variation-in-cingulate-anatomy-comment-on-lieberman-eisenberger-2015-and-yarkoni/ doi = 10.6084/m9.figshare.2026014) -- it's hard to tell just looking at a single sag slice (tho i appreciate the semi-transparent colors; just to give you some context for my comment: if i go to a point that seems by eye to be squarely in your preSMA ROI's (MNI 3/20/42) the HO atlas reports 76% paraCg gyrus, 13% ant div of the Cg gyrus, and 2% frontal gyrus. so i would not be inclined to label it pre-SMA. if you at the flat map in PALOMERO-GALLAGHER JCN '08 or some of the chapters in Vogt's book, it's

consistent with this general idea that MCC extends more dorsally than many seem to appreciate.

likewise, given Vogt's work cited in the intro, is 'pgACC' more appropriate than 'rACC'; are 'a/pMCC' more appropriate than 'dACCc/r'? you might make a case for rACC, because the Wager group has consistently used this term across many, many papers for a decade, but the others not so much.

- fig 3 could be added as the first panel of fig 2, given that this is how the depicted regions were determined

- "dorsal posterior midcingulate cortex; the
252 middle zone included portions of pre-SMA as well as much of dorsal anterior cingulate (dACC) running along the corpus callosum (Vogt, 2005);"

this is a funny mishmash of terms. some of them seem inconsistent with the terms used in the figure. Vogt has strongly argued for dropping the term dACC; how were these anatomical labels generated exactly? Mai atlas? Havard-Oxford ROI's? Vogt papers cited in the intro? Ongur-Carmichael-Price papers cited in the intro? something else? this should be defined and (internally) consistent.

- "Vorobiev V, Luppino G (1998) Parcellation of human mesial area 6: cytoarchitectonic evidence
631 for three separate areas. :1-5."

is the wrong citation; see http://onlinelibrary.wiley.com/doi/10.1046/j.1460-9568.1998.00236.x/pdf ; same comment applies when you cite it in the discussion

- "and two ventral clusters consistent caudal and
263 rostral dACC (Vogt, 2005). Within"

I imagine Dr. Vogt's face growing very red reading this. See esp his chapter in the book discussing the proliferation of non-std terms for MCC/ACC sub-regions

- "Within the middle functional zone, we identified two clusters dorsal to the cingulate sulcus
262 consistent with pre-SMA (Picard and Strick, 1996)"

look at figures 4-6 in that seminal paper; note how dorsal the activations in fig 4 are (clustered around Z =~ 55ish); if i pick something similar in MNI152 (3/15/55), then HO reports 53% SFG, 18% paracingulate, 5% juxtapositional lobule. again, my point is that I'm not sure that pre-SMA is the most appropriate label.

in short, "Thus, the boundaries of
266 the clusters we identified exclusively using a functional co-activation based approach converged
267 with many distinctions previously drawn on the basis of anatomical criteria." does not sit well with me.

- "psychological concepts"

topics, to be consistent

- figure 4 is lovely but it's tough to see any of the subcortical structures. you could add labels, but switching to coronals or coronals and labels would probably be more helpful

- "Colored voxels indicate significantly greater co-activation with the seed region of the same
A) Functional zones
B) Sub-regions
z= -15 z=-3 z=9 z=21 z=33 z=45 z=57
De La Vega 17
color (at right) than other regions in the same map."

"map" is unclear; you really mean whatever term you are using for the 3 larger parcels, right?

- "regions previously associated with chemosensory
304 processing (Rolls et al., 1990; Yaxley et al., 1990) and reward-driven learning (Schoenbaum and
305 Roesch, 2005)."

a little dated.....see also Tom Stalnaker's excellent recent review on OFC function

- "To test if MFC zones"

'whether'

- "The middle zone was primarily associated with various facets of cognitive control, but
333 was also implicated in negative affect-pain and fear - as well as decision-making"

:)

- fig 5 is very, very cool. i really like the dots and overall lay out. but, the colors on the polar plots don't quite match the brain maps. for instance, the 'red' region at the bottom is linked to a burgundy/magenta colored trace.....the yellow and brown are also pretty off elsewhere in the fig. you can probably fix this in adobe illustrator pretty easily using the eyedropper

also, consider dropping 'specialization' from the legend; 'preferences' or simply 'profiles' is probably better

- "while activity in rostral pre-SMA and dACC"

whereas

- "that "dorsal ACC" is important for the integration of negative 406 affect into cognitive control
407 (Shackman et al., 2011),"

shackman prefers "MCC"

'into' should be "pain, and"

for what it's worth, I am absolutely fine with beating up on the adaptive control hypothesis - Tor and Tal do it all the time. we did the best we could

given the existing evidentiary record (which, of course, goes way beyond imaging studies).

having said that, i don't really buy the statement that "our findings suggest a substantial functional-anatomical specificity not accounted by such theories."

first, in our 2011 paper we noted specificity in the MFC:
"We rejected claims of strict functional segregation because our CBMA demonstrated that imaging studies of negative affect, pain and cognitive control consistently activate an overlapping region in aMCC (Fig. 2) and because ACC (the putative 'affective division' of the cingulate) was not preferentially associated with negative affect or pain. Nevertheless, the results of the CBMA are consistent with a measure of functional specialization across rostral cingulate (Fig. 1c). For example, the CBMA indicated that only studies of negative affect consistently activated subgenual ACC (sgACC; see Supplementary information S1 (box)). Likewise, the elicitation of negative affect and pain consistently activated pregenual ACC (pgACC) and posterior MCC (pMCC), whereas cognitive control did not."

second, the results of the present analysis (e.g. figure 5, bottom panel), which rely on reverse inference, are consistent with our earlier claim, based (in part on the forward inference), that negative affect ('fear'), pain, and cognitive control ('conflict' and 'inhibition') all consistently engage the anterior MCC. (this is also evident in the maps shown in http://www.talyarkoni.org/blog/2015/12/14/still-not-selective-comment-on-comment-on-comment-on-lieberman-eisenberger-2015/).

third, the results presented here indicate even less functional specificity than was implied by the more focused (or 'biased' or 'theory driven') analyses reported by Shack '11. after all, the authors show that reward also engages MCC (something considered only in passing by Shack (see his Box 3)).

if anything, you would be on safer ground saying that
1. the present results are broadly consistent with Shack '11. Remember, he identified his ROI using a completely different approach, which yielded a ROI that seems to lie at the intersection of the yellow, green, and red subdivisions of the 'middle' zone (see the bottom panel of my fig 2). to my knowledge, there's nothing about the co-activation based parcellation that makes it more 'real' than partitioning based on meta-analytic overlap. so, an apples to apples comparison suggests that, if you focus on the aMCC, our results are pretty consistent.
2. BUT, the authors should feel comfortable claiming that the present results extend Shack '11 in a number of important ways and then detail those (e.g. much more comprehensive survey of anatomy [all of MFC] and of psychology)

as an aside, on p 23, line 407, you might consider citing this https://www.ncbi.nlm.nih.gov/pubmed/24787485, which provides an updated version of our perspective

- authors go on to write that in the discussion: "Although all four middle MFC sub-regions were significantly 409 associated with aspects of cognitive control...the two pre-SMA subregions [yellow + green] showed greater associations with cognitive 411 control processes-in particular WM...In contrast, dACC sub-regions [red + purple] were more strongly 413 associated with affect, with caudal dACC showing a stronger affinity for pain, while rostral 414 dACC showed a greater association with decision-making."

the corresponding section of the results reads, "In the middle zone, activity in all four sub-regions was predicted by aspects of cognitive control...and pain ...dACC clusters [red + purple] were further characterized by a strong association with affect-- including fear and reward."

i have a couple of concerns about this section beyond those mentioned a moment ago.

a generic, broadband concern stems from the issues raised in Yarkoni's recent blog: authors need to be very careful w/ claims of 'specificity' derived from NSynth

a second concern is that the authors are in danger of interpreting the null, because (if I understand things correctly) they did not perform contrasts that would license the statements in the discussion about 'more' and 'greater'.

having said that, i am entirely comfortable with the authors making claims that the middle zone is not functionally homogeneous because their results clearly make that point. these two ideas are not inconsistent: diverse psychological states (fear, pain, and neg affect) can all engage aMCC *and* there can be differences in the strength of association across the middle zone. remember, in 2011 we noted that "First, our meta-analysis demonstrates that aMCC is consistently activated at the subdivision level by manipulations of negative affect, pain and cognitive control. [Additional research]...will be required to determine whether negative affect and pain are anatomically coincident with cognitive control at finer levels of resolution, are intermingled (as some early imaging studies suggest157, 158, 159) or are organized along overlapping gradients44, 160, 161, 162."

i think the present report is a wonderful example of that kind of additional research starting to come to fruition, and an important extension of our earlier work.

as another aside - I'm certainly *not* advocating that the lead author do this or that the PI's encourage it, but if you want an apples to apples comparison, you *could* perform a very interesting and informative supplementary analysis using the mask from Shackman et al NRN 2011, which can be freely downloaded at http://neurovault.org/collections/474/.

- "Our results are in contrast with accounts of cognitive control that hypothesize dACC to
416 be the MFC region primarily responsible for conflict processing."

again, i think you are over-selling. figure 5 shows that inhibition and conflict engage all 4 divisions of the middle zone, which seems consistent with extant models to me.

- "our results support an
417 alternate hypothesis in which negative affective signals that indicate conflict may be initially
418 processed in dACC and are integrated in pre-SMA with high-level goals"

it is not clear how the results depicted in fig 5 (pain and cog conflict are associated w/ all 4; whereas fear is only significantly associated with the 2 more ventral dACC subdivisions) motivate this claim.

- "Our findings are consistent with previous single-cell recording in macaques

that
420 primarily show conflict related activity in cells in pre-SMA and not dACC (Nakamura and
421 Roesch, 2005; Cole et al., 2009)."

based on the evidence reviewed in https://www.ncbi.nlm.nih.gov/pubmed/24787485, including invasive recordings in humans, i think this claim is far too strong at best. this concern is amplified by my concern, detailed earlier, that the ROI's labeled as 'pre-SMA' are inferior to the likely probabilistic location of pre-SMA.

- jess' last name is hyphenated

- "Despite the additional functional-anatomical specialization that we observed within MFC, 446 it is notable that no region in MFC is selectively activated by a single psychological concept. At 447 least two distinct concepts significantly predict activation in each cluster, even at the relatively 448 stringent permuted threshold of p<0.001."

this strikes me as an extremely important point and consistent with the TDW's recent comment that 'There need not be only one.' We and others have also made this point e.g. http://shackmanlab.org/wp-content/uploads/2015/06/shackman_BBS2015corrected.pdf note that,

"brain regions can dynamically
assume different roles. Just as an individual can perform psychologically distinct roles in different social networks (e.g., executive,
mother, sister, daughter), brain regions are poised to perform a
range of functions (a property termed functional "superimposition")
in different neural "contexts" corresponding to their level of participation
in particular functional networks. To paraphrase Pearson and
colleagues (Pearson et al. 2014), key brain regions, such as the orbitofrontal cortex, are functionally heterogeneous, with individual
neurons dynamically multiplexed into different functional roles. As
such, they will "evade a single, modular, functional role assignment"
(p. 954). Our brain reflects evolutionary pressures that demanded
distributed neural systems capable of using information about pleasure
and pain, derived from stimuli saturated with hedonic and motivational
significance, to adaptively regulate attention, learning,
somatic mobilization, and action in the service of maximizing reproductive fitness."

i would recommend breaking this idea out into a new section of the discussion, not burying it in 'Anterior Zone' (likewise for future challenges section)

- "least two distinct concepts"
topics

- "even at the relatively
448 stringent permuted threshold of p<0.001." i worry that this is over-selling....is it?

- "(Lieberman and
452 Eisenberger, in press)." should prob cite her Ann Rev paper as well

- "While our large-scale meta-analytic approach allowed us to comprehensively synthesize a

454 plethora of fMRI findings, there are several limitations."

Despite this progress, a number of important challenges remain for future research

- "Second, the quality of
460 activation data in Neurosynth is inherently limited due to its automatically generated nature."

need to be more specific and briefly unpack, as in Wager's essay on L&E 2015 (figure 2)

- "and the large-scale nature of our
463 approach (N= 9,721) ameliorates these concerns."

no it doesn't. just look thru the papers you actually get for particular locations or topics. the size of the DB does not ameliorate this concern

- "Moreover, as with any meta-analysis of fMRI
464 data, our approach is limited by the low spatial resolution of fMRI"

this is really 2 points mushed into one. first, as concerns bold fmri, the source of signal is uncertain (logothetis) and the resolution after smoothing is on the order of 6+mm. not cellular level. second, as concerns meta, the problem is aggravated because of the information that is discarded when you 'peakify' clusters and then smooth the foci in meta-analytic space. see http://psych.colorado.edu/~tor/Papers/Salimi-Khorshidi_2009_pain_meta_analysis_comparison.pdf for a nice discussion.

in sum, one key challenge for future research would seem to be to assess the hypotheses generated by the very interesting present study in a single sample of subjects scanned performing diverse tasks.

- "and the inability to
465 disentangle individual differences in anatomy across subjects. In particular, it is difficult to
466 precisely localize each of our clusters onto gyri and sulci; this is particularly problematic in
467 dACC, where BA 32' lies only a few millimeters dorsal of BA 24, and shows large anatomical
468 variation across humans (Paus, 2001; Cole et al., 2009)."

this is addressed here http://shackmanlab.org/the-importance-of-respecting-variation-in-cingulate-anatomy-comment-on-lieberman-eisenberger-2015-and-yarkoni/ doi = 10.6084/m9.figshare.2026014

the authors can adequately address this concern by using probabilistic atlas labels and clearly describing their method for labeling

the language about architectonic areas is beside the point (at least until Zilles releases the Juelich maps for ACC/MCC) given the authors emphasis on functionally (ie meta-analytically) defined regions, right?

- "While only advances in MR technology
469 will improve spatial resolution,"

what about single subject fmri analyses, analyses w/o exogenous smoothing

kernels, invasive recordings?

- "Yet in our approach they did so to a very substantial degree."

per my earlier comments, i think this is not quite correct

- "There is a need for comprehensive efforts to identify functional
23 subregions with distinct functional profiles across these diverse processes."

why? what is driving this need exactly?

- "the middle zone with cognitive control and negative affect and the
34 anterior with internal mentation and affective processing."

missing comma; what about reward in the middle zone?

- "revealing greater
36 functional diversity than previous "unifying" accounts of MFC might suggest."

per my earlier remarks, the accounts you actually mention (aside from L&E15) are not meant to be unifying accounts of MFC. as you note elsewhere, each is narrower in scope than that. you do a disservice to this beautiful data w/ remarks of this sort. better to emphasize that this study extends prior accounts in a number of important ways.

this on the other hand is almost perfect: "This study provides a comprehensive functional map of the human medial frontal cortex using relatively unbiased data-driven methods." you could even drop the caveat about 'relatively unbiased'

- given the comment about open sharing, i was surprised that there was no mention of sharing these maps (or the code) w the community, as that would massively enhance the ultimate significance and value of these analyses.

- "Acknowledgments: R01MH096906 National Institutes of Health." that's it? really? across 3 NIH funded labs?

Reviewer #2 (Rationale for Significance Rating (Required)):

see below

Reviewer #2 :

This report presents a medial frontal cortex subdivision based on co-activation with external areas in fMRI studies. There are already a number of studies which subdivided MFC based on microscopic, biochemical or connectional features. However the authors base this subdivision on task-related co-activation of MFC voxels as derived from "Neurosynth", a neuroimaging database of about 10,000 studies.
They identify three larger scale sub-areas (anterior, middle, posterior MFC) and nine smaller subregions. In a second step they look at the subregion's co-activation profile and look at the psychological terms and concepts that lead to an activation in these regions.
This study could be a quite helpful addition to previous MFC subdivisions.

However the authors need to convince the reader that on the one hand their findings are indeed in line with the numerous previous anatomical MFC subdivisions, but on the other hand where they add insight to exactly this sizeable literature.

More specifically these questions remain:

The authors stress repeatedly the alignment of their findings with previous anatomical MFC studies "to a very substantial degree". Could they be more specific and provide evidence for this assertion. Does the number of clusters align with previous findings? However then I would expect them to find e.g., three distinct cingulate motor areas (as for example Dum & Strick). Or do the authors think that the spatial extend and location of their sub-areas resonates with previous research? Would they be able to demonstrate this? Or does their functional specialization analysis align with previous neurophysiological studies?

What does their method of using data-mining fMRI activation peaks to the above mentioned sizeable literature on MFC sub-specialisation? I presume that their method does not allow for finer-grained sub-divisions than cyto-architecture, receptor density or tracer injection based studies? If they wanted for a function-based subdivision could they not have used a "functional localizer" approach as Amiez and Petrides (2014)?

I am not sure if I follow the assertion: "Although the 12-cluster solution results in a marginally better silhouette score, this comes at the cost of additional complexity." Why would they discard this solution if it fits the criteria that they themselves set better? If they think that MFC organization is indeed more complex why would this be a cost?

Are there contextual differences in co-activation patterns? E.g., dACC appears to co-activate with DLPFC and amygdala. It also appears to be associated with conflict, decision making and pain. Is it more activated with the amygdala in studies that mention pain and more activated with DLPFC in studies that mention conflict?

Even though the authors state distinct areas with distinct functions and connections there appear to be strong overall similarities in neighboring regions in co-activation and function potentially with gradients of change along different axes. For example "motor" seems to gradually decrease from posterior to anterior. Pain appears to decrease from ventral to dorsal Similarly DLPFC co-activation appears to increase from posterior to anterior. It would be very interesting to see if there is concordance or correlation in these functional - connectivity gradients / changes? E.g., a gradient of decrease in pain is associated with a decrease in amygdala co-activation?

Why does the three-zone subdivision group together regions with vastly different cyto-architecture and separate regions with similar cyto-architecture?

Minor things:

How well did the Harvard Oxford grey matter match the implicit Neurosynth data-base grey matter? I suppose all Neurosynth foci should lie in the grey matter? What percentage of Neurosynth foci are outside the 30% Harvard-Oxford grey matter atlas?

	Line 67: "what about connectivity based" Line: 84 "raising questions about their whether these regions are selectively involved in specific mental functions" 377: "and then directing linking them to psychological function"