A Manuscript Microscope 'Sentence Audit' of:

Transcriptional-Regulatory Convergence Across Functional MDD Risk Variants Identified by Massively Parallel Reporter Assays

What is the Manuscript Microscope Sentence Audit?

The Manuscript Microscope Sentence Audit is a research paper introspection system that parses the text of your manuscript into minimal sentence components for faster, more accurate, enhanced proofreading.

Why use a Sentence Audit to proofread your manuscript?

- Accelerated Proofreading: Examine long technical texts in a fraction of the usual time.
- Superior Proofreading: Detect subtle errors that are invisible to traditional methods.
- Focused Proofreading: Inspect each individual sentence component in isolation.
- Reliable Proofreading: Ensure every single word of your manuscript is correct.
- Easier Proofreading: Take the hardship out of crafting academic papers.

Bonus 1: Improved Productivity: Rapidly refine rough drafts to polished papers.
Bonus 2: Improved Authorship: Cultivate a clear, concise, consistent, writing style.
Bonus 3: Improved Reputation: Become known for rigorously precise publications.

Manuscript Source: https://www.biorxiv.org/content/10.1101/2021.03.05.434177v1

Manuscript Authors: Bernard Mulvey & Joseph D. Dougherty

Audit Date: 22/03/21 **Audit Identifier:** LD04C842AJQ95KF **Code Version:** 3.6

Features of the Sentence Audit:

The Sentence Audit combines two complementary proofreading approaches:

1. Each sentence of your text is parsed and displayed in isolation for focused inspection.
2. Each individual sentence is further parsed into Minimal Sentence Components for a deeper review of the clarity, composition and consistency of the language you used.

The Minimal Sentence Components shown are the smallest coherent elements of each sentence of your text as derived from it's conjunctions, prepositions and selected punctuation symbols (i.e. commas, semicolons, round and square brackets).

The combined approaches ensure easier, faster, more effective proofreading.

Comments and Caveats:

• The sentence parsing is achieved using a prototype natural language processing pipeline written in Python and may include occasional errors in sentence segmentation.

• Depending on the source of the input text, the Sentence Audit may contain occasional html artefacts that are parsed as sentences (E.g. "Download figure. Open in new tab").

• Always consult the original research paper as the true reference source for the text.

Contact Information:

To get a Manuscript Microscope Sentence Audit of any other research paper, simply forward any copy of the text to John.James@OxfordResearchServices.com.

All queries, feedback or suggestions are also very welcome.

Research Paper Sections:

The sections of the research paper input text parsed in this audit.

Section No.	Headings	Sentences
Section: 1	ABSTRACT	11
Section: 2	INTRODUCTION	16
N/A	--- --- --- --- --- --- ---	0
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The Sentence Audit Of The Research Paper

Title # Transcriptional-Regulatory Convergence Across Functional MDD Risk Variants Identified by Massively Parallel Reporter Assays

S1 [001] ABSTRACT

S1 [002] Family and population studies indicate clear heritability of major depressive disorder (MDD), though its underlying biology remains unclear.

Family ...
... and population studies indicate clear heritability ...
... of major depressive disorder ...
... (MDD), ...
... though its underlying biology remains unclear.

S1 [003] The majority of single-nucleotide polymorphism (SNP) linkage blocks associated with MDD by genome-wide association studies (GWASes) are believed to alter transcriptional regulators (e.g., enhancers, promoters), based on enrichment of marks correlated with these functions.

The majority ...
... of single-nucleotide polymorphism ...
... (SNP) ...
... linkage blocks associated ...
... with MDD ...
... by genome-wide association studies ...
... (GWASes) ...
... are believed ...
... to alter transcriptional regulators ...
... (e.g., enhancers, ...
... promoters), ...
... based ...
... on enrichment ...
... of marks correlated ...
... with these functions.

S1 [004] A key to understanding MDD pathophysiology will be elucidation of which SNPs are functional and how such functional variants biologically converge to elicit the disease.

A key ...
... to understanding MDD pathophysiology will be elucidation ...
... of which SNPs are functional ...
... and how ...
... such functional variants biologically converge ...
... to elicit the disease.

S1 [005] Furthermore, retinoids can elicit MDD in patients, and promote depressive behaviors in rodent models, acting via a regulatory system of retinoid receptor transcription factors (TFs).

Furthermore, ...
... retinoids can elicit MDD ...
... in patients, ...
... and promote depressive behaviors ...
... in rodent models, ...
... acting ...
... via a regulatory system ...
... of retinoid receptor transcription factors ...
... (TFs).

S1 [006] We therefore sought to simultaneously identify functional genetic variants and assess retinoid pathway regulation of MDD risk loci.

We therefore sought ...
... to simultaneously identify functional genetic variants ...
... and assess retinoid pathway regulation ...
... of MDD risk loci.

S1 [007] Using Massively Parallel Reporter Assays (MPRAs), we functionally screened over 1 000 SNPs prioritized from 39 neuropsychiatric trait/disease GWAS loci, with SNPs selected based on overlap with predicted regulatory features—including expression quantitative trait loci (eQTL) and histone marks—from human brains and cell cultures.

Using Massively Parallel Reporter Assays ...
... (MPRAs), ...
... we functionally screened ...
... over 1 000 SNPs prioritized ...
... from 39 neuropsychiatric trait/disease GWAS loci, ...
... with SNPs selected based ...
... on overlap ...
... with predicted regulatory features—including expression quantitative trait loci ...
... (eQTL) ...
... and histone marks—from human brains ...
... and cell cultures.

S1 [008] We identified >100 SNPs with allelic effects on expression in a retinoid-responsive model system.

We identified >100 SNPs ...
... with allelic effects ...
... on expression ...
... in a retinoid-responsive model system.

S1 [009] Further, functional SNPs were enriched for binding sequences of retinoic acid-receptive transcription factors (TFs); with additional allelic differences unmasked by treatment with all-trans retinoic acid (ATRA).

Further, ...
... functional SNPs were enriched ...
... for binding sequences ...
... of retinoic acid-receptive transcription factors ...
... (TFs); ...
... with additional allelic differences unmasked ...
... by treatment ...

... with all-trans retinoic acid ...

... (ATRA).

S1 [010] Finally, motifs overrepresented across functional SNPs corresponded to TFs highly specific to serotonergic neurons, suggesting an in vivo site of action.

Finally, ...

... motifs overrepresented ...

... across functional SNPs corresponded ...

... to TFs highly specific ...

... to serotonergic neurons, ...

... suggesting an in vivo site ...

... of action.

S1 [011] Our application of MPRAs to screen MDD-associated SNPs suggests a shared transcriptional regulatory program across loci, a subset of which are unmasked by retinoids.

Our application ...

... of MPRAs ...

... to screen MDD-associated SNPs suggests a shared transcriptional regulatory program ...

... across loci, ...

... a subset ...

... of which are unmasked ...

... by retinoids.

S2 [012] INTRODUCTION

S2 [013] Major depressive disorder (MDD) is a common but debilitating psychiatric disorder affecting hundreds of millions worldwide1, exacting substantial tolls on both individuals2 and societies3.

Major depressive disorder ...

... (MDD) ...

... is a common ...

... but debilitating psychiatric disorder affecting hundreds ...

... of millions worldwide1, ...

... exacting substantial tolls ...

... on both individuals2 ...

... and societies3.

S2 [014] Despite the global burden of MDD, nearly half of patients do not clinically respond to treatment4, in part due to limited understanding of its biological underpinnings.

Despite the global burden ...

... of MDD, ...

... nearly half ...

... of patients do not clinically respond ...

... to treatment4, ...

... in part ...

... due to limited understanding ...

... of its biological underpinnings.

S2 [015] Family studies have demonstrated that MDD risk is at least 30% heritable5,6.

Family studies have demonstrated ...
... that MDD risk is ...
... at least 30% heritable5,6.

S2 [016] More recently, genome-wide association studies (GWASes) have demonstrated similar estimates for severe MDD7, and have helped narrow in on associated single nucleotide polymorphisms (SNPs)8–12, a tantalizing entry point for understanding the biology of MDD.

More recently, ...
... genome-wide association studies ...
... (GWASes) ...
... have demonstrated similar estimates ...
... for severe MDD7, ...
... and have helped narrow ...
... in ...
... on associated single nucleotide polymorphisms ...
... (SNPs)8–12, ...
... a tantalizing entry point ...
... for understanding the biology ...
... of MDD.

S2 [017] However, GWAS studies do not identify causal variants, but rather implicate wider co-inherited regions consisting of many SNPs in linkage disequilibrium (LD).

However, ...
... GWAS studies do not identify causal variants, ...
... but rather implicate wider co-inherited regions consisting ...
... of many SNPs ...
... in linkage disequilibrium ...
... (LD).

S2 [018] Most disease-associated SNPs are found outside of protein-coding sequences suggesting probable roles in transcriptional regulation (TR)13–16.

Most disease-associated SNPs are found outside ...
... of protein-coding sequences suggesting probable roles ...
... in transcriptional regulation ...
... (TR)13–16.

S2 [019] However, this leaves unresolved issues of identifying which linked SNPs have functional allelic impacts on TR, and how these act together across loci to result in disease.

However, ...
... this leaves unresolved issues ...
... of identifying ...
... which linked SNPs have functional allelic impacts ...
... on TR, ...
... and how these act together ...
... across loci ...
... to result ...

End of Sample Audit

This is a truncated Manuscript Microscope Sample Audit.

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