Resting-State Neuronal Oscillatory Correlates of Working Memory Performance

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Abstract

Purpose: Working memory (WM) represents the brain’s ability to maintain information in a readily available state for short periods of time. This study examines the resting-state cortical activity patterns that are most associated with performance on a difficult working-memory task.

Methods: Magnetoencephalographic (MEG) band-passed (delta/theta (1–7 Hz), alpha (8–13 Hz), beta (14–30 Hz)) and sensor based regional power was collected in a population of adult men (18–28 yrs, n = 24) in both an eyes-closed and eyes-open resting state. The normalized power within each resting state condition as well as the normalized change in power between eyes closed and open (zECO) were correlated with performance on a WM task. The regional and band-limited measures that were most associated with performance were then combined using singular value decomposition (SVD) to determine the degree to which zECO power was associated with performance on the three-back verbal WM task.

Results: Changes in power from eyes closed to open revealed a significant decrease in power in all band-widths that was most pronounced in the posterior brain regions (delta/theta band). zECO right posterior frontal and parietal cortex delta/theta power were found to be inversely correlated with three-back working memory performance. The SVD evaluation of the most correlated zECO metrics then provided a singular measure that was highly correlated with three-back performance (r = −0.73, p<0.0001).

Conclusion: Our results indicate that there is an association between WM performance and changes in resting-state power (right posterior frontal and parietal delta/theta power). Moreover, an SVD of the most associated zECO measures produces a composite resting-state metric of regional neural oscillatory power that has an improved association with WM performance. To our knowledge, this is the first investigation that has found that changes in resting state electromagnetic neural patterns are highly associated with verbal working memory performance.

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Introduction

Working memory (WM) consists of several interacting brain processes that are involved in both maintaining and manipulating information for short periods of time [1,2].

The neural mechanisms contributing to WM have been a major focus of the neurosciences, with progress in this field being applied to investigations of a wide array of brain pathologies, education, learning, as well as furthering our basic understanding of the brain [2–8].

The ability to selectively attend to relevant information has been described as the capacity to focus our cognitive resources to our goals. Selective attention is thought to be a major facet of working memory that engages relevant sensory networks and inhibits irrelevant brain networks [9–12]. Some investigators suggest that selective attention and WM are supported by common neural mechanisms [2,12,13]. Investigations into these mechanisms have found that lapses in selective attention are associated with neurophysiological changes in cortical processing [13]. Both selective attention and physiological arousal, which has previously been described as an energetic state at a point in time, have been linked to the prefrontal and parietal cortices, suggesting that there may be a functional overlap between these two processes [12,14–16]. Decreased levels of cortical arousal also appear to correlate with performance on cognitive tasks [15]. Thus, it appears that either task-related lapses in attention or decreased levels of cortical
arousal can be detected physiologically and are linked to decreased cognitive performance [14,15].

The importance of selective attention and arousal in working memory has been further strengthened by recent hemodynamic investigations showing associations between resting-state brain patterns and working memory performance [17–20]. Sala-Llonch et al. have hypothesized that resting-state brain activity may regulate top-down selective attention and arousal, which prepare brain networks for WM functions [19]. These studies suggest that markers of spontaneous neural activity during the resting state may allow for the measurement of selective attention and arousal networks, and thus predict WM proficiency.

Recent research demonstrates that magnetoencephalography can be used to detect correlated networks of brain activity during working memory [21–23]. The current study investigated resting-state cortical arousal and selective attention using magnetoencephalography (MEG). We hypothesized that individuals demonstrating higher levels of cortical arousal and higher levels of selective attention during a pre-task resting state would perform better on a subsequently performed WM task. As the optimal measures of both selective attention and arousal were not known, all regional measurements and band-limited (delta/theta, alpha, beta) cortical power measurements were used to determine if certain patterns of resting-state brain activity were associated with WM performance. Both the eyes-open and eyes-closed resting state were used, as it was also unclear which condition would be more associated with WM proficiency. Finally, we calculated the regional and band-limited changes in normalized power between the eyes closed and open conditions to identify individual differences in neural activity in the absence of visual stimulation. We hypothesized that a metric reflecting the changes in cortical activation and arousal occurring between eyes closed and open would provide additional information regarding each individual’s resting-state cortical function. These resting-state neurophysiological measures were then compared to WM performance to determine whether MEG-detected resting-state cortical activity was associated with WM performance.

Materials and Methods

Participants

The data were obtained from 24 adult male participants (1 left handed, Age: 18–28, Avg. = 22 yrs, Std = 3.0 yrs). All participants took part in this study after submitting signed informed consent. No participant had a history of psychiatric or neurologic conditions, trauma, or substance abuse. One subject was removed from the study as an outlier due to performance (three-back d’ >3 std dev. away from group d’ mean (see experimental protocol below)). Experimental procedures were approved by the University of California, San Diego (UCSD) Human Research Protection Program.

Experimental Protocol

Before data collection, the study protocol was explained to each participant so that they were aware a working memory task would follow the resting state conditions, but they were not explicitly instructed to prepare for the task. To assess resting-state activity, participants were first asked to rest quietly with their eyes closed for four minutes and were then asked to fixate on a back-illuminated screen for another four minutes. This process was then repeated to obtain a total of 8 minutes in each resting-state condition. Both continuous video camera surveillance and real-time monitoring of MEG recordings for slow wave generation were used to ensure no participants fell asleep during the experimental protocol.

The subsequently performed verbal n-back WM task, adapted from Braver et al., was used to provide a metric of working memory performance [24]. Task stimuli consisted of letters presented on the same back projection screen as above using Presentation 14.5 (Neurobehavioral systems inc.; Albany, CA). Participants performed two blocks of each of four conditions serially with a rest period between blocks. In the zero-back condition, included as a control because of minimal WM requirements, participants responded by raising the right index finger when a pre-specified letter appeared. In the one-back condition, participants indicated when the stimulus on the screen matched the previous letter by raising their right index finger. During the two-back condition participants were instructed to indicate when the presented stimulus matched the letter presented two before, and the three-back task similarly asked participants to respond when the stimulus matched the third previous letter (Figure 1). Responses were recorded using a non-metallic touchpad (Elekta-Neuromag, Helsinki, Finland). Behavioral response data was combined with stimuli presentation data on a single output channel. Matlab 10 b (Mathworks Inc, Natick, MA) was then used to perform automated behavioral analysis that was then verified by manual observation.

Each block consisted of 100 trials with each stimulus being presented for 500 ms and 1.5 seconds being allowed for response before the next stimulus. The duration between the onset of subsequent stimuli was 2 seconds regardless of participant responses. There was a short training session prior to each new condition. Each block of trials lasted roughly four minutes. Across conditions, true target stimuli accounted for 30% (3% std dev.) of all presented stimuli. Performance was evaluated using the d prime (d’) measure, which is the difference between the z-scores of the true positive rate and false positive rate. d’ = z(hit rate)- z(false alarm rate). Statistical analyses were calculated using Matlab 10 b as well as SPSS (v12.0, SPSS, Inc. Chicago, IL). Data can be obtained by contacting the corresponding author (Heister).

MEG Data Acquisition

MEG activity was recorded continuously for the duration of the resting-state conditions by a VectorView whole-head MEG system (Elekta-Neuromag, Helsinki, Finland), using the 204 gradiometer channels in an enhanced multi-layer magnetically shielded room (IMEDCO-AG, Hагendorf, Switzerland) [25]. MEG data were acquired at 1000 Hz with a hardware band-pass filter at 0.1–330 Hz. Data were first visually inspected for large sources of noise and truncated to remove the first and last 10 seconds of data from each file. The signal space separation with temporal extension (SSST) package (MaxFilter) was applied to all MEG recordings to remove residual artifacts due to eye movements and/or cardiac signals [26,27]. Independent component analysis was also performed to remove remaining eye-blink and cardiac signals. Precautions were taken to ensure head stability; foam wedges were inserted between the subject’s head and the inside of the unit, and a Velcro strap was placed under the subject’s chin and anchored in superior and posterior axes. The head positions were measured before each session and we ensured that the head movement across different sessions was less than 5 mm (usually 2–3 mm).

Signal Processing

MEG data were collected in the eyes-open and eyes-closed conditions. Power analyses were conducted for the MEG data using Finite impulse response (FIR) filtering separated into bandwidths: delta/theta (1–7 Hz), alpha (8–13 Hz), and beta
(14–30 Hz). All band-passed signals used edges consisting of 10% of each limit (e.g. 1–4 Hz used 0.1 and 0.4 Hz edges). Power amplitude was calculated by squaring the absolute value of the discrete time analytical signal obtained via the Hilbert transform of each band-passed signal. Power measurements for each channel were then averaged across each experimental block (roughly 4 minutes, as described above). Brain regions were separated into 10 cortical areas (i.e. left and right anterior-frontal, posterior-frontal, temporal, parietal, and occipital) based on sensor locations.

Power Analysis and Performance Correlation
Regional power measurements in each (1–7 Hz, 8–13 Hz, 14–30 Hz) frequency band-passed signal were analyzed across the two conditions (eyes-open vs. eyes-closed). Before correlating these measurements with working memory performance signals were normalized by subtracting the mean and dividing by the standard deviation across all subjects in each band and region (z-score). To compare resting-state conditions, the eyes-open power was subtracted from the eyes-closed power in each region and band for each individual. Subsequently, each comparison was then z-score normalized across subjects. This metric was thus a z-score of the eyes-closed minus eyes-open power (zECO).

Initial attempts to separate the delta/theta band into two bands found that the power in smaller frequency ranges did not correlate as well with performance. The Pearson correlation coefficient was used to calculate which condition, region, and band-limited measures were most correlated with working-memory performance.

Singular Value Decomposition
Makeig and Jung (1995) have previously established that electroencephalographic changes that relate to performance during an attention task can be isolated to a single principal component [28]. In a similar fashion, we hypothesized that our sensor based regional MEG recordings may reflect overlapping cortical processes and that performing a singular value decomposition (SVD) of our data had the advantage of finding the dominant pattern in this data and also to reduce the number of comparisons in our analysis. The SVD is a data-driven process that allows for the factorization of a data set matrix defined as $X$ into orthogonal components and is calculated as follows:

$$X = USV^T$$

$X$ is a data matrix with $M$ rows and $N$ columns that is then decomposed into a $U$ matrix ($M \times N$) that provides the best approximation of the column data in a lower rank for each mode. $V^T$ is the transposed $V$ matrix ($N \times N$) that provides the best approximation of the row data in a lower rank for each mode. The diagonal components of the $S$ matrix ($N \times N$) are the singular value scaling factors for each mode and are arranged in descending order. SVD is similar to principal component analysis in that if each data column is normalized with a mean of zero, $U*S$ of the SVD is equal to the principal component scores.

Results
Working Memory Performance
Mean $d'$ progressively decreased as the n-back task became more difficult (zero-back: 5.7±0.7, one-back: 4.5±0.2, two-back: 3.3±0.1, three-back: 2.3±0.0; $p<0.001$ for all pairwise comparisons; Figure 2A). Individually sorted accuracy and $d'$ measures in each condition revealed that three-back performance was the most appropriate condition for stratifying individuals according to working-memory proficiency as it had no ceiling effect and displayed the most linear distribution of performances (accuracy linear regression fit: zero-back $r^2 = 0.46$; one-back $r^2 = 0.66$; two-back $r^2 = 0.85$; three-back $r^2 = 0.93$; $d'$ linear regression fit: zero-back $r^2 = 0.50$; one-back $r^2 = 0.98$; two-back $r^2 = 0.81$; three-back $r^2 = 0.89$; Figure 2B, 2C). While both the three-back accuracy scores and $d'$ measures were found to have linear distributions, the three-back, $d'$ measure was used as a metric for working memory performance because it evaluated the ability of our subjects’ to identify correct stimuli without the influence of positive or negative response bias [29].

Regional and Band Changes from Eyes Closed to Eyes Open
Further analyses were next conducted on condition, regional, and frequency band-limited power measurements. An initial inspection of the data found no significant difference between hemispheres in any frequency band ($p>0.05$). Thus, data were collapsed across hemispheres for these group analyses. A 2-factor repeated measures ANOVA was performed to test for changes in
power across regions (anterior frontal, posterior frontal, temporal, parietal, occipital) and conditions (eyes open and eyes closed) for each frequency band. The Huynh-Feldt correction was used to adjust for heterogeneity of variance in multiple degrees-of-freedom tests. Figure 3 displays graphs of the results. In the delta/theta band, there was a significant interaction of region and condition effects ($p < 0.001$). Power significantly decreased in all regions in the eyes open relative to the closed condition (anterior frontal: $2173 \text{ fT}^2/\text{cm}^2$, $p < 0.05$; posterior frontal: $2786 \text{ fT}^2/\text{cm}^2$, $p < 0.01$; temporal: $364 \text{ fT}^2/\text{cm}^2$, $p < 0.001$; parietal: $1119 \text{ fT}^2/\text{cm}^2$, $p < 0.001$; occipital: $1326 \text{ fT}^2/\text{cm}^2$, $p < 0.001$). In the alpha band, there was a significant interaction of region and condition effects ($p < 0.001$). Power was also significantly decreased in the eyes open relative to the closed condition (temporal: $263 \text{ fT}^2/\text{cm}^2$, $p < 0.001$; parietal: $2120 \text{ fT}^2/\text{cm}^2$, $p < 0.01$; occipital: $2405 \text{ fT}^2/\text{cm}^2$, $p < 0.001$). The beta band also exhibited a significant interaction between condition and region ($p < 0.001$), with regional decreases in the eyes open relative to closed condition (temporal: $492 \text{ fT}^2/\text{cm}^2$, $p < 0.001$; parietal: $271 \text{ fT}^2/\text{cm}^2$, $p < 0.001$; occipital: $492 \text{ fT}^2/\text{cm}^2$, $p < 0.001$).

**Figure 2.** A: Mean Performance (± standard error). Performance significantly decreased with increasing task difficulty. B: Individual subject accuracy for each n-back condition. The three-back condition has a more linear distribution than the other two conditions and no ceiling effect (linear regression fit: zero-back $r^2 = 0.46$; one-back $r^2 = 0.66$; two-back $r^2 = 0.85$; three-back $r^2 = 0.93$). C: Individual subject $d'$ for each n-back condition. (linear regression fit: zero-back $r^2 = 0.58$; one-back $r^2 = 0.98$; two-back $r^2 = 0.81$; three-back $r^2 = 0.89$) ** = $p < 0.01$, Bonferroni corrected.

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Correlations of Cortical Power and WM Performance

Figure 4 displays the Pearson correlation $r$ value for each band-limited comparison of neuronal activity and WM performance in all resting conditions as compared to both two-back and three-back $d'$ performance. While there were several interesting associations as described below, no individual comparison in either the eyes-open or eyes-closed conditions survived Bonferroni multiple comparisons correction for significance. The two-back comparisons did not show any significant correlations but are included to allow for comparison with three-back data. In the three-back eyes-open comparison, performance was inversely associated with delta/theta power in both the left and right occipital regions. In the three-back eyes-closed comparison, alpha and beta power in the bilateral frontal and left temporal regions was mildly positively associated with working memory performance. Additionally, several regions in the delta/theta band exhibited inverse associations with three-back WM performance.

Next we correlated WM performance with the normalized difference in power between the eyes closed and open conditions ($zECO$). Figure 4 found that delta/theta $zECO$ power in multiple regions had a mild inverse non-significant association with two-back performance. Figure 4 demonstrates that increases in delta/theta $zECO$ power in many regions negatively correlated with WM performance, but the right posterior frontal and parietal regions were found to have significant correlations that survived Bonferroni correction ($r = -0.72$, $p < 0.05$ with Bonferroni correction; $r = -0.696$, $p < 0.05$ with Bonferroni correction; $df = 22$, respectively). Thus, individuals with better three-back WM performance showed little change or decreases in right posterior frontal and parietal delta/theta $zECO$ power.

Selection of Condition

We next aimed to quantitatively establish which resting state condition measurements were most associated with working memory performance. Due to a lack of significant two-back comparisons, only the three back comparisons were further analyzed. The $r$ values of all regions in the three-back delta/theta and beta bands were combined within each condition. The alpha band was excluded from further analysis due to the lack of a discernible power/performance trend (Figure 4). This analysis found that the $zECO$ $r$ values had significantly larger negative correlations than either eyes open or closed conditions alone.
Selection of Regions most Correlated with Performance

Next we sought to identify the regions and frequency-limited comparisons that most correlated with three-back WM performance. In order to identify the region and band measures that were most highly correlated with performance, the absolute value of region and band correlation \( r \) values were converted to band-limited z-scores. Regions in the delta/theta band and beta band that were more than 1 standard deviation from the remainder of the band-limited comparisons were selected. These criteria isolated the right posterior frontal and right parietal regions in the delta/theta band, and the right posterior frontal region in the beta band.

Performance Classifications

In order to further evaluate changes in power and working memory performance, participants were then separated into WM three-back performance-based groups: high performers (highest 25% of population; \( d' \geq 2.67 \) \( n = 6 \)), and low performers (lowest 25% of population; \( d' \leq 2.1 \) \( n = 6 \)). The normalized mean power of the regions and bands that were most associated with performance as described above were then compared between these two performance groups to show the differences in cortical activity in these regions between groups. Low performers and high performers were observed to have similar eyes-open power in these selected regions, but low performers had increased power during the eyes-closed state, while high performers exhibited decreases in power in the eyes-closed state. This resulted in zECO values that were much higher in low performers than high performers (\( p < 0.001 \)) (Figure 5B, 6A demonstrates selected regions that were most highly associated with WM performance).

SVD Analysis

We found that the comparisons most associated with performance were from neighboring brain regions. As such, these measures contained overlapping information that can be more clearly demonstrated using SVD, which isolates the dominant patterns in the data and produces an individual resting-state metric. This metric was more highly associated with WM...
performance than any individual comparison. We first used the selection criteria described above to identify the region and frequency zECO power measurements that most correlated with performance (Figure 6A).

An SVD was then performed using the normalized power across subjects from these three comparisons (1–7 Hz right posterior frontal and parietal, 14–30 Hz right posterior frontal). This compiled data formed a 24×3 data matrix (24 subjects × 3 selected band/region comparisons) that was then decomposed into a 24×3 U matrix (subjects × modes), a 3×3 singular value matrix, and a 3×3 transposed V matrix (selected band/region comparisons × modes).

Evaluation of the singular (S) value for each mode revealed that 59% of the variance in the data was present in the first mode, whereas only 35% and 6% of the variance were in the second and third modes, respectively. Correlating the weighting arrays from each mode revealed that the first mode highly correlated with WM performance ($r = -0.732$) in contrast to the second ($r = -0.038$) and the third modes ($r = -0.084$). Thus, the performance-related variance in the data appears to be restricted to the first mode (Figure 6B). The resulting first mode of the U matrix was found to be mildly more correlated with the three-back d’ measure than the single most correlated comparison (right posterior frontal $r = -0.72$ versus the SVD first mode $r = -0.73$, $p<0.0001$, df = 22, Figure 6C, 6D). The negative correlation of the SVD values and WM d’ indicates that lower-performing subjects had larger decreases in power from eyes closed to open in the right posterior frontal and parietal regions whereas higher-performing subjects tended to show little change or increases in power from eyes closed to open in the posterior frontal and parietal regions (Figure 6D).

To establish that this effect is not a result of the three lowest performers, this analysis was then repeated with these three subjects removed and the Pearson correlation remained significant ($r = -0.63$, $p<0.005$, $n = 21$).

Discussion

Resting-state measures can be useful for understanding individual differences in the variability of resting-state cortical activity and perhaps the extent to which resting-state cortical activity contributes to cognitive functioning, including WM. To our knowledge, this is the first study to show that individual changes in delta/theta power (1–7 Hz; right posterior frontal and parietal regions) from eyes closed to eyes open are highly associated with performance on a subsequent three-back WM task. Furthermore, changes in power from eyes closed to open in select regions can be combined into the most dominant (i.e. first) mode of an SVD to provide a singular resting-state measure that is more highly associated with WM performance than any individual measure.

An association of resting-state cortical activity and WM performance has previously been observed using hemodynamic and neurophysiological markers [17–19,30–32]. More specifically, some investigators reported that resting-state activation in the parietal region is consistently linked to an attention network and n-back performance [19,33–35]. Activation in the right frontal and parietal regions have previously been linked to the engagement of visuospatial processing and selective attention [19,33–39]. Additionally, neurophysiological measures of selective attention and cortical arousal (e.g. larger delta/theta and beta power) are associated with WM performance and WM capacity [2,13,15,39–43].

Our results demonstrated that individuals with poorer three-back WM showed larger increases in right posterior frontal and parietal delta/theta from eyes closed to open conditions. In contrast, higher performing subjects tended to have less change or a decrease in power in these regions across resting-state conditions (Figure 5B). These findings are consistent with prior investigations suggesting that patterns of resting-state brain activity in the right posterior frontal and parietal regions may be markers for the engagement of selective attention or cortical arousal. While selective attention has classically been considered to be focused on external perceptual inputs, it has recently been proposed that this entity can also be directed toward internal processes as well [9,10]. We suggest that lower cortical arousal was associated with both higher eyes closed delta/theta power in our selected regions and also associated with lower WM performance. We speculate that the variability of the normalized change in power across resting states may result from the engagement of internal selective attention or increased cortical arousal occurring in high WM performers in the eyes open fixation task.

Figure 5. A: r values for all regions across conditions show a larger inverse correlation and a decrease in positive correlation in the zECO conditions. B: Using the most highly correlated normalized band and region comparisons (delta/theta right posterior frontal, delta/theta right parietal, beta right posterior frontal), high performers and low performers exhibit large differences in the zECO power across resting-state conditions. * = Bonferroni corrected p < 0.05. ** = Bonferroni corrected p < 0.01. *** = single comparison p < 0.001. doi:10.1371/journal.pone.0066820.g005
As there were several neighboring brain regions that correlated with performance, we found that the association between resting-state cortical processes and WM performance was strengthened by using the dominant pattern in the data across multiple regions via SVD. While the SVD did not provide dramatic improvements in the power associations, it proved useful for combining several resting-state measurements into a single measure that was more highly associated with performance than any one regional or band limited measure. SVD is a data driven method that searches for the dominant patterns in the data while, isolating unrelated variation to less dominant modes, and minimizes the problem of multiple comparisons.

Previous groups have found that tonic alpha power, phasic alpha power, and peak alpha frequency correlated with working memory processing and performance, while the current investigation found very little correlation between performance and resting state alpha power [41,44–45]. This discrepancy is likely the result of previous investigations using power recorded during the task while this study was interested in resting state power and behavior correlations. Furthermore, differences in methodology (i.e. electroencephalography versus magnetoencephalography) based, different cognitive measures of working memory, and different population demographics make direct comparisons of our data with prior investigations difficult [46].

The results of this investigation were also inconsistent with a recent EEG study that found a small but significant positive correlation between an eyes-closed resting state relative theta power, and performance on an attention and recall task [47]. We suggest that this may in large part be due to our use of MEG data from young adult males (mean 22 years of age) versus the use of EEG data from an elderly population (mean = 61 years of age) comprising more than 60% females. These results suggest that while certain resting-state measures may be associated with performance, the regional and band-limited measures and level of association of these measures are likely dependent on population demographics and working memory task employed.

Initial attempts to separate the delta/theta band into two separate bands revealed that some participants produced this behavioral correlation in the lower (1–4 Hz) band whereas other subjects showed this correlation in the higher (4–7 Hz) band. These initial analyses failed to show that lower and higher bands differentiated the low and high WM performers. Moreover, these groups could not be separated on the basis of demographic characteristics or performance metrics. Thus, our data indicated that the physiological effect we were measuring extended across both bands in our population and a compiled 1–7 Hz band was the optimal measure for our purposes.

Previous studies have found measures of both cortical arousal and selective attention affect cognitive performance, and our findings that resting-state power measures are associated with WM performance is consistent with these prior investigations, although direct measurements of arousal or selective attention were not collected in this study [42,48–50]. Prior investigations into the role of the eyes open versus closed states have suggested that changes in alpha power were related to cortical arousal and changes in delta, theta, and beta power were more related to cortical activation [49]. This would suggest that it is the differential cortical activation of various resting state brain networks and not cortical arousal that has functional implications on cognitive task performance. More studies will be necessary to clarify the neural mechanisms leading to the strong correlation of WM task performance and changes in right posterior frontal and parietal power from eyes closed to open.

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Author Contributions

Conceived and designed the experiments: DH MD SN OT DLH TS RL MH. Performed the experiments: AR AA DH. Analyzed the data: DH SN RL MH. Wrote the paper: DH MD SN OT DLH TS RL MH. Contributed reagents/materials/analysis tools: DH MD SN OT DLH TS RL MH. Performed the experiments: AR AA DH. Analyzed the data: DH SN RL MH. Wrote the paper: DH MD SN DLH RL MH.

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