Potential Conflicts of Interest

Nothing to report.

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Reply

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We recently reported a correspondence between event-related potential (ERP)-based evidence of bottom-up attention and command following among patients with severe brain injury.[1] The P3a ERP reflects bottom-up attention and is often obtained by comparing responses to nontarget deviant and standard stimuli.[2] The P3b ERP reflects top-down attention and is often obtained by comparing responses to target deviant and standard stimuli.[2] In our article,[1] we quantified bottom-up attention by comparing responses to all deviant stimuli—target and nontarget—and all standard stimuli. In their letter, Bonfiglio and Carboncini highlight that our ERP definition comprises both P3a and P3b components and postulate that top-down attention may underlie our reported relationship between command following and ERP-based evidence of attention.

Our contrasts delineate a hierarchy of cognitive abilities. We quantified bottom-up attention by comparing all deviant and standard trials. This contrast has more statistical power than the conventional P3a contrast, because more deviant trials are available. Furthermore, we quantified top-down attention by directly comparing target and nontarget deviant trials. This approach was necessary because a deviant stimulus is only a target in our paradigm if the participant selectively attends to that deviant stimulus when instructed. If the participant does not comply with task instructions, however, the conventional P3b contrast (target vs standard) could return a significant effect driven by attentional orienting to deviant stimulation. This concern is particularly relevant for the patients in our investigation who could not overtly confirm that they understood and followed task instructions.

To examine any differences between the two approaches, we conducted the P3a and P3b comparisons described by Bonfiglio and Carboncini. These comparisons yielded findings consistent with our original report[1]; we detected P3a effects from all healthy volunteers and all patients who demonstrated command following, and we did not detect P3b effects from any of the patients. The conventional P3b contrast yielded a higher hit-rate in our healthy volunteers (100%) than our original approach (67%); this likely results from the greater depth of processing elicited by targets relative to standards, as compared with targets relative to nontargets. However, as explained above, the conventional P3b contrast does not necessarily isolate top-down attention in our paradigm.

Bonfiglio and Carboncini also propose an explanatory role of cognitive attitudes in command following, which could be quantified using blink-related electroencephalogram (EEG)[3,4] or functional magnetic resonance imaging (fMRI)-based activation of particular cortical networks. We cannot directly investigate this proposal, because our EEG and fMRI data were not collected simultaneously. However, the evidence linking intrinsic networks to external awareness adds weight to their hypothesis.[5]

Author Contributions

All authors contributed equally to this work.

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Nothing to report.

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Two Patients with *TNK2* Mutations and Late Onset Infantile Spasm

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In a 2013 article in the *Annals of Neurology*, Yuki Hitomi et al identified a homozygous variant in *TNK2* as the causative mutation of 3 severe autosomal recessive infantile onset epilepsy patients in 1 family.[1] However, definitive proof of pathogenicity will require identification of further homozygote or compound heterozygote mutations in individuals with a similar phenotype. We now report 2 patients with similar findings, establishing mutations in *TNK2* as a genetic cause of severe autosomal recessive infantile onset epilepsy.

Patient A is a 20-month-old nondysmorphic girl of healthy nonconsanguineous parents. At 13 months of age, she started to have spasm seizures refractory to various antiepileptic drugs, and her cognition regressed significantly soon after seizure onset. Adrenocorticotropic hormone controlled the seizures completely, but spasm relapsed after 6 months of treatment. Brain magnetic resonance imaging was normal, whereas 24-hour electroencephalogram showed hypsarrhythmia. The patient and her parents were sequenced by whole exome sequencing and analyzed by Clinical Sequencing Analyzer (WuXi NextCODE, Cambridge, MA), and a pair of compound heterozygote variants in *TNK2* (c.2860 G>T, c.3004 G>T) were found and verified by Sanger sequencing.

Patient B is an 18-month-old girl and the second of 3 children of healthy parents. At the age of 11 months, she exhibited seizure activity characterized by clusters of spasms. Various antiepileptic drugs and ketogenic diet had no effect to seizures. Trio-based whole exome sequencing and analysis found a pair of compound heterozygote variants in *TNK2* (c.1705 A>G, c.2243 G>A), which were verified by Sanger sequencing.

The previously reported proband was a girl of 31 months who had focal seizures since age 19 months. Cognitive regression occurred soon after seizure onset.[1] She also developed autistic features. Her younger brother developed epilepsy at the age of 21 months, with focal seizures. Early development was normal, but speech and cognitive regression occurred soon after epilepsy onset.[1] Our finds confirmed that *TNK2* mutations can cause severe autosomal recessive infantile onset epilepsy and expand the phenotype to infantile spasm.

Author Contributions

S.Q. and J.P. contributed to the conception and design of the study; W.C., G.L., and Y.Z. contributed to the acquisition and analysis of data; X.M. and Y.Z. drafted the text.

Potential Conflicts of Interest

Nothing to report.

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Reply

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We thank Mao et al for their report on the identification of compound heterozygous mutations in the *TNK2* gene in 2 unrelated patients with infantile onset refractory epileptic spasms. In our previous publication, we reported a homozygous *TNK2* mutation in 3 of 3 children of nonconsanguineous parents with severe, infantile onset focal epilepsy and cognitive regression, along with supporting functional studies.[1] Despite sequencing efforts in large cohorts of patients with epilepsy during recent years, no other mutations in *TNK2* have been reported so far. The findings of Mao et al lend further support to our initial hypothesis that recessive mutations in the *TNK2* gene may play a role in severe forms of infantile onset epilepsy. Furthermore, the current report expands the phenotypic spectrum associated with *TNK2* mutations to also include infantile spasms, which was not a feature in our family. However, we believe that these findings should be interpreted with caution in light of recent observations that arose after the publication of the Exome Aggregation Consortium (ExAc) data, which were unavailable at the time of our original publication.[2] We now know that *TNK2* ranks among the top 25% most tolerant genes in the genome, translating to a relatively large number of polymorphic functional variants observed in this gene in the general population.[3] Given this observation, the identification of compound heterozygote mutations is not that unexpected. Conversely, we did not identify any compound heterozygote