A fundamental element in the spatial structure of Megalopolis is a hierarchy of cities connected by a network of roads. Running along the central spine of the region, from south to north are cities of major importance including Washington DC, Baltimore, Philadelphia, New York, and Boston. Around these cities are large suburban expanses as well as a range of smaller cities including Trenton, Newark, New Haven, Providence, Manchester and Portland.

The region is crisscrossed with interstate highways that allow quick connections. The Interstate Highway System was created in 1956. Under the legislation the federal government pays 90% of the cost. Some of the longest interstates pass through the region. Interstate 90 runs 3081 miles from Boston to Seattle and I-80 covers 2907 miles from New York City to San Francisco. The central north-south route, I-95 runs all the way down the east coast of the US.

While the interstates connect the region to other parts of the country they also play an important part in the dispersal from the central cities. Interstates that circle the cities such as the famous Beltway in DC, I-495, I-695 around Baltimore or I-95 around Boston have allowed longer commuting patterns and the dispersals of commerce and people. The interstates have facilitated a wider spread of people and economic activity across the region.

Designed to make traffic move quickly and easy, the interstates have also generated more traffic. To be stuck on the Beltway, or any of the many other bottlenecks, in a traffic jam is a reminder of the tremendous amount of traffic in the region.